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The Longitudinal Trajectory of Subclinical Manic Symptoms from Childhood to Adolescence and their Predictive Validity for Bipolar Disorder

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**The Longitudinal Trajectory of Subclinical Manic Symptoms from
Childhood to Adolescence and their Predictive Validity for
Bipolar Disorder**

EFSTATHIOS PAPACHRISTOU

**A thesis submitted in partial fulfilment of
the requirements for the degree of Doctor of
Philosophy**

**Section of Psychosis Studies
Institute of Psychiatry
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University of London**

July 2013

Abstract

Background

Bipolar Disorder (BD) is one of the leading causes of disability worldwide. Much of the disability associated with BD is linked to the early onset of the disorder, typically between 16 and 30 years of age. The aim of the PhD was to examine whether subclinical manic symptoms are associated with subsequent onset BD and to identify the longitudinal trajectories associated with conversion to syndromal BD.

Methods

I analyzed data from TRAILS (TRacking Adolescents' Individuals Lives Survey), a prospective population based study of 2,230 Dutch adolescents. Participants were assessed with the Child Behaviour Checklist 6-18 (CBCL 6-18) at ages 11, 13 and 16 years and were administered the Composite International Diagnostic Interview (CIDI) at age 19. The prevalence rate for BD in TRAILS was 5.4%.

Results

I developed and validated a new scale, the Child Behaviour Checklist-Mania Scale (CBCL-MS) to capture subclinical manic symptoms. The CBCL-MS consists of 19 items of the CBCL 6-18 selected by an expert panel to map onto the DSM criteria for Mania. The CBCL-MS had a four factor structure that was interpretable and temporally stable, and presented with good reliability and discriminative ability for BD. Based on assessments with the CBCL-MS at age 11, a Latent Class Analysis extracted three classes, representing an asymptomatic class (n=862), a mildly symptomatic class (n=845) and a highly symptomatic class (n=199). Membership in the highly symptomatic class was associated with a 7-fold increase in the odds for subsequent BD. Non-conversion to BD for members of this class was characterised by a decreasing longitudinal trajectory of subclinical manic symptomatology.

Conclusions

These results support the concept of “alarm symptoms” in BD, as highly deviant childhood manic symptoms were associated with a subsequently greatly elevated risk of BD, and for initiatives to identify underlying BD at an earlier and more amenable stage. However, there was little support for a detectable prodromal phase for BD.

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Brief table of contents

- Title page	1
- Abstract.....	2
- Acknowledgements	4
- Brief table of contents	5
- Detailed table of contents	6
- Schedule of tables.....	14
- Schedule of figures	16
1 Expanding Conceptual Frameworks: Life course Risk Modelling for Mental Disorders ^a	18
2 Life Course Approach for Bipolar Disorder	44
3 Study Population.....	70
4 Child Behavior Checklist - Mania Scale (CBCL-MS): Development and Evaluation of a population-based screening scale for bipolar disorder ^b	84
5 Alarm Symptoms in the Early Diagnosis of Bipolar Disorder: A Population Based Cohort Study ^c	128
6 Trajectories to Bipolar Disorder from Childhood to Adulthood ^d	161
7 Discussion.....	191
Appendix	206

^a Papachristou E, Frangou S, Reichenberg A. (2012). Expanding conceptual frameworks: Life course risk modelling for mental disorders. *Psychiatry Research*. 206(2-3): 140-145

^b Papachristou E, Ormel J, Oldehinkel AJ, Kyriakopoulos M, Reinares M, Reichenberg A, Frangou S. (2013). Child Behavior Checklist - Mania Scale (CBCL-MS): Development and validation of a population-based screening scale for bipolar disorder. *PlosONE*. (in press)

^c Alarm Symptoms in the early diagnosis of bipolar disorder: a population based cohort study. Submitted to *The American Journal of Psychiatry*

^d Manuscript prepared for submission to *JAMA Psychiatry*

Detailed table of contents

Abstract.....	2
Acknowledgments	4
1 Expanding conceptual frameworks: Life course risk modelling for mental disorders	
<i>(Published in Psychiatry Research)</i>	18
Title page	19
Abstract.....	19
1.1 Introduction	20
1.2 Life course approaches in epidemiology	21
1.2.1 Critical periods	21
1.2.2 Accumulation of risk	22
1.3 Life course approaches within the psychiatric epidemiological	
research	23
1.3.1 Critical periods	24
1.3.2 Accumulation of risk	25
1.3.3 Traditional multivariate analyses vs. advanced statistical	
modeling techniques.....	26
1.4 Directions for future research	29
References	31

2 Life course approach for bipolar disorder	44
2.1 Introduction	44
2.1.1 Clinical features of bipolar disorder.....	44
2.2.2 Personal and societal burden	44
2.2 Prevalence of Bipolar Disorder	45
2.2.1 Lifetime prevalence of BD.....	45
2.2.2 Prevalence in Youth	46
2.3 Bipolar Disorder across the lifespan	47
2.3.1 Age-dependent manifestations	47
2.3.2 Illness severity in relation to age of onset.....	49
2.3.3 Psychiatric comorbidities.....	50
2.3.4 Differential Diagnosis of BD	51
2.3.5 The concept of prodrome in bipolar disorder	52
References	54
 3 Study Population.....	 70
3.1 Introduction	70
3.2 Overview of the Tracking Individuals Lives Survey (TRAILS).....	70
3.3 Ethics	72
3.4 The analytic cohort	72
3.5 Instruments	75
3.5.1 Outcome Measures.....	75
3.5.1.1 The World Health Organization (WHO) Composite	

International Diagnostic Interview (CIDI)	75
3.5.1.2 CBCL	75
3.5.2 Additional Measures	77
3.5.2.1 Family History of Psychopathology	77
3.5.2.2 Socioeconomic Status	78
3.5.2.3 Family Functioning	78
3.5.2.4 Cognition	79
3.6 Missing Data	79
References	81
 4 Child Behavior Checklist - Mania Scale (CBCL-MS): Development and evaluation of a population-based screening scale for Bipolar Disorder (published in PlosONE)	 84
Title page	85
Abstract	86
Introduction	87
Methods	90
Participants	90
Assessments	90
Child behaviour Check List-Mania Scale (CBCL-MS)	90
Statistical analysis	91
Reliability and validity of the CBCL-MS	91

Sensitivity and Specificity of the CBCL-MS.....	92
Results	94
TRAILS participants with BD.....	94
Internal consistency and factor structure of the CBCL-MS	94
Discriminative ability and performance of the CBCL-MS	94
Discussion	97
Prevalence and characteristics of TRAILS participants with BD	97
Reliability and validity of the CBCL-MS.....	97
Factor structure of the CBCL-MS reveals developmentally meaningful dimensions of liability to BD	98
Discriminative ability of the CBCL-MS	99
Methodological issues and future directions	101
References.....	104
Tables	113
Figures	115
Supplemental Material.....	118
Selection of items	118
Psychometric properties of CBCL-MS across ages.....	118
Discriminative ability of the CBCL-MS	123
Representativeness of the TRAILS sample.....	124
Data availability.....	125
References	125

Appendix.....	126
Child Behaviour Checklist (CBCL-MS).....	126
CBCL-MS scoring sheet	127
 5 Alarm Symptoms in the early diagnosis of bipolar disorder: a population based cohort study (<i>Submitted to the American Journal of Psychiatry</i>)	128
Title page	129
Abstract	130
Introduction.....	131
Methods	133
TRAILS cohort.....	133
Instruments.....	133
Child Behavior Checklist Mania-Scale (CBCL-MS)	133
Computer Assisted Personal Interview version 20 (CAPI) 239	
of the Composite International Diagnostic Interview	134
Wechsler Intelligence Scale for Children-Revised	
(WISC-R)	134
General Functioning Subscale of the McMaster Family	
Assessment Device (FAD-GFS)	134
Parental psychiatric morbidity.....	135
Parental socioeconomic status	135
Statistical analysis	135

Results	137
Classification of TRAILS cohort members at age 11 based on the CBCL-MS.....	137
Association of class membership with demographic and risk factors	137
Class membership at age 11 and risk for subsequent BD	138
Class membership at age 11 and risk for subsequent non-BD disorders	138
Alarm symptoms for BD.....	139
Discussion	140
Empirically derived classification based on degree and pattern of manic symptoms.....	140
Implications for the early detection of Bipolar Disorder	140
Methodological considerations	142
Conclusions	142
References.....	144
Tables	149
Figures	151
Supplemental Material.....	154
A. Representativeness of the TRAILS sample	154
B. Development of the Child Behaviour Checklist-Mania Scale (full details in Papachristou et al. PloSONE 2013).....	154

C. Details of Parental Morbidity in the TRAILS sample.....	157
D. Characteristics of patients with Bipolar Disorder per class.....	158
E. Positive Predictive Value of “Alarm Symptoms” for Cancer.....	158
References	159

6. Trajectories to Bipolar Disorder from childhood to adulthood 161

Title Page.....	162
Abstract.....	163
Introduction	165
Methods.....	167
Participants and Procedures	167
Classification of TRAILS participants based on the CBCL-MS at age 11 years	168
Statistical Analysis	168
Results.....	170
Asymptomatic Class	170
Mildly Symptomatic Class	171
Highly Symptomatic Class	171
CBCL-MS changes proximal to syndromal onset of BD irrespective of class.....	171
Discussion	172
References	175

Tables	179
Figures.....	181
Supplemental Material	183
Representativeness of the TRAILS sample.....	183
Development of the Child Behavior Checklist-Mania Scale (full details in Papachristou et al., PLoS ONE 2013).....	183
Psychometric properties and discriminative value of the Child Behavior Checklist-Mania Scale	185
Characteristics of patients with Bipolar Disorder per class	190
7. Discussion	191
7.1 Introduction	191
7.2 Summary of the main findings.....	191
7.3 Strengths and limitations.....	193
7.3.1 Strengths	193
7.3.2 Limitations.....	194
7.4 Integration of findings.....	195
7.5 Future directions.....	197
7.6 References	199
- Appendix	206

Schedule of tables

4.1 Child Behavior Checklist-Mania Scale items and corresponding core and extended DSM-IV criteria for Mania.....	113
4.2 Child Behavior Checklist-Mania Scale total and Factor Scores in TRAILS participants with Bipolar Disorder (BD) and healthy participants	114
4.S1 Items, factors and item loadings of the CBCL-MS at age 16.....	120
4.S2 Items, factors and item loadings of the CBCL-MS at age 13.....	121
4.S3 Items, factors and item loadings of the CBCL-MS at age 11.....	122
4.S4 Discriminative ability of the total CBCL-MS and its factors	123
4.S5 Regression models	124
4.S6 Characteristics of TRAILS participants at enrolment compared to the 2001 national census data available online from the Centraal Bureau voor de Statistiek (www.cbs.nl)	124
5.1 Frequency of endorsement of Child Behavior Checklist- Mania Scale (CBCL-MS) at age 11 years.....	149
5.2 Fit indices for 1-5 Class solutions.....	150
5.3 Effect of covariates on class membership	150
5.S1 Characteristics of TRAILS participants at enrolment compared to the 2001 national census data available from the Centraal Bureau voor de Statistiek (www.cbs.nl)	154
5.S2 Child Behavior Checklist- Mania Scale items and corresponding core and extended criteria for Mania.....	155
5.S3 Parental Psychiatric Morbidity in the TRAILS sample	157

5.S4 Characteristics of cases with syndromal BD by age 19 according to class membership at age 11.....	158
5.S5 Positive Predictive Value of “Alarm Symptoms” for Cancer.....	158
6.1 Characteristics of TRAILS members and BD cases according to class Membership at age 11.....	179
6.2 Probability of parental endorsement of CBCL-MS items per class.....	180
6.S1 Characteristics of TRAILS participants at enrolment compared to the 2001 national census data available online from the Centraal Bureau voor de Statistiek (www.cbs.nl)	183
6.S2 Child Behavior Checklist-Mania Scale items and corresponding core and extended criteria for Mania	185
6.S3 Items, factors and item loading of the CBCL-MS at age 16	187
6.S4 Items, factors and item loading of the CBCL-MS at age 13	188
6.S5 Items, factors and item loading of the CBCL-MS at age 11	189
6.S6 Characterstics of cases with syndromal BD by age 19 according to class membership at age 11.....	190

Schedule of figures

1.1 Critical periods of risk exposure and cumulative interactions of risk factors for psychotic illness: an illustrative example of the most pertinent findings	42
1.2 Differences in the developmental course of cognitive functions from childhood to early adolescence with schizophrenia: an illustrative example	43
3.1 Sampling Procedure of TRAILS	73
3.2 Attrition Rates in TRAILS	74
4.1 Factors and factor loadings of the Child Behavior Checklist (CBCL-MS)	115
4.2 Receiver Operating Characteristics curve of the Child Behavior Checklist-Mania Scale for Bipolar Disorder vs. healthy TRAILS participants.....	116
4.3 Child Behavior Checklist-Mania Scale Scores in TRAILS Participants	117
4.S1 Scree Plot of parallel analysis at age 16.....	119
5.1 Child Behaviour Checklist- Mania Scale (CBCL-MS)	151
5.2 Cognitive, Socioeconomic, and Family Characteristics of the Asymptomatic, Mildly Symptomatic and Highly Symptomatic Classes.....	152
5.3 Specificity of the Association of Class membership to syndromal BD	153
6.1 The factor structure of the CBCL-MS	181
6.2 CBCL-MS course by class and outcome	182

6.S1 Scree plot of parallel analysis at age 16.....	190
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1 Expanding conceptual frameworks: Life course risk modelling for mental disorders

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Expanding conceptual frameworks: Life course risk modelling for mental disorders

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Abstract

Psychiatric epidemiology has made significant contributions to the identification of risk factors for mental disorders. Available evidence underscores the complexity of the interactions between risk and disease and highlights conceptual and methodological challenges particularly in examining risk and disease relations beyond the level of simple associations. We propose that a life course approach in the study of risk factors for mental disorders, combined with fast developing analytical statistical tools, is the most promising avenue towards shifting the focus of the field from associations to generating and testing aetiological hypotheses. This review presents the basic tenants of life course risk modelling, highlights key examples in the available literature that demonstrate the potential of this approach to advance our understanding of the trajectories from risk to disease and discusses priorities for future research.

Keywords: epidemiology; critical periods; cumulative risk; latent class analyses; growth models

1. Introduction

Psychiatric epidemiology and especially analytical epidemiological studies have made great advances in identifying multiple risk factors for mental disorders, particularly for schizophrenia, mood disorders and anxiety disorders. Across diagnostic categories key risk factors include low Socioeconomic Status (SES) (Danese et al., 2009), familial psychopathology (Lichtenstein et al., 2009), Stressful Life Events (SLEs) (Kendler, Karkowski, & Prescott, 1999), low IQ (Koenen et al., 2009), family dysfunction (Bouma et al., 2008) and cannabis use (Degenhardt et al., 2007). Although informative, these reports are commonly limited to simple associations between a risk exposure and a later adverse mental health outcome while the timing and exact mechanism of this transition remain largely unstudied. Here we advocate a life course approach in the study of risk factors for mental disorders as this has the potential to advance our understanding of the trajectories from risk to disease.

Within the current cohort designs, life course formulations have the potential to shed light in the mechanisms as well as the timing of exposures underlying the development of psychopathology, especially when combined with the appropriate analytical statistical tools. The objectives of this article are threefold: a) to complement recent reviews on early risk factors and genetic variants for common mental disorders, e.g. schizophrenia (Brown and Derkits, 2009), by highlighting the additional value of the life course approach; b) to present the basic concepts of life course risk modelling; and c) to highlight key examples for its usefulness for medicine, psychiatry and public health. The examples presented provide evidence on how the life course approach can serve as the starting point in addressing questions about mechanisms mediating between risk and disease outcome on a more fundamental level. Finally, we make specific suggestions as to how life course modelling can be more fully integrated into psychiatric epidemiological research. Such information is crucial in moving the field from an associative focus to generating and testing aetiological hypotheses.

2. Life Course Approaches in Epidemiology

The life course approach was mostly developed within the field of cardiovascular medicine from which we draw key examples to illustrate its two basic tenants, namely critical periods and accumulated risk (Lynch and Smith, 2005).

2.1 Critical Periods

Life course models recognise that the timing of exposure plays an important role in determining the risk for disease. In this context life course models focus on critical or sensitive periods. The critical period model assumes that there are stages in human development during which the influence of external agents may have crucial effects that cannot be altered by subsequent events and precipitate disease in later life. Conversely, the influence of the same agents during any other developmental stage will be minimal or absent. Implicit in the critical period model is the notion that the influence of external agents, when it occurs during this particular stage, alters the function or structure of biological tissues or systems through processes of “biological programming” so that the effect of the exposure becomes “embodied” (Kuh et al. 2003). In contrast, sensitive periods are stages in development when the influence of external agents may have the strongest effect on disease risk that could be however modified by subsequent experiences or exposures (Kuh et al 2003). At this particular junction, the distinction between critical and sensitive periods is often blurred as the basic biological effects of exposures that could result in altered “biological programming” are poorly understood. For simplicity and parsimony we will refer to all models focusing on the timing of exposures as critical period models.

The best evidence for the critical period concept derives from the foetal origin hypothesis in cardiovascular medicine. It proposes that adversity very early in pregnancy, and especially poor maternal nutrition, leads to impaired growth and biological programming of the foetus, thus increasing the risk of cardiovascular disease

later in life (Barker, 1995; Barker and Clark, 1997; Barker and Osmond, 1986; Eriksson et al., 2001; Painter et al., 2006). The incidence of Coronary Artery Disease (CAD) is increased following exposure to famine in the first trimester of gestation but not if exposure to famine occurs in mid- or late gestation (Painter et al. 2006).

2.2 Accumulation of Risk

The accumulation of risk model suggests that exposures or insults act in a cumulative fashion to gradually increase the risk of disease or mortality. This hypothesis postulates that cumulative differential life time exposure is the main explanation for observed individual differences in disease risk (Kuh et al., 2003). Numerous studies have examined the risk accumulation hypothesis in relation to medical outcomes, health inequalities and social, physical and cognitive functioning (Power et al., 1996; Lynch et al., 1997; Smith et al., 1997; Hart et al., 1998; Power et al., 1999; Holland et al., 2000; Wamala et al., 2001). There are two main variations to the risk accumulation hypothesis relating to whether there is prolonged exposure to a single risk factor or an interaction between multiple factors either in an additive (risk clustering) or in a sequential fashion (chains of risk) (Kuh et al. 2003).

A typical example for the prolonged exposure model was provided by Smith and colleagues (1997). They employed a prospective observational study design with a 21 year follow-up focusing on mortality. They examined the risk of lower SES at three time points, in childhood based on father's occupation and in early and late adulthood respectively based on own first and more established occupation. They found a cumulative effect of lower SES acting over the lifetime; people who reported belonging to the low SES group at a single measurement point had a relative death rate of 1.29 (95% CI 1.08-1.56) which increased further to 1.71 (95% CI 1.46-2.01) for those reporting belonging to the low SES group at all three measurement points. Similarly, Wamala et al (2001) report that, in women, early and late socioeconomic advantage are respectively associated with a 2.48 (95% CI 0.90-6.83) and a 3.22 (95% CI 1.02-10.53)

increase in the risk for Coronary Heart Disease (CHD). However, women with both early and late exposure had an even greater risk of 4.22 (95% CI 1.4-12.1).

We now focus on how risk factors may interact to increase risk. Different risk factors may cluster together and may act cumulatively to increase risk. For example, Luchsinger et al (2005) demonstrated by following 1,138 individuals for 5.5 years that diabetes, hypertension, heart disease, and smoking were all associated with a higher risk of Alzheimer's disease. In a subsample of people in high risk for Alzheimer's Disease ($N=246$) the risk conferred by the risk factors individually ranged from 1.4 to 3.6 (adjusted for age and gender). The hazards ratios of the interactions between these factors varied greatly and were highest for the interaction of diabetes and smoking which reached 13.7 (95% CI 1.8-101.7).

Alternatively, risk factors may be linked forming chains of risk or insults whereby each exposure may lead to further adverse exposures or experiences. Each link in the chain may have an independent effect on disease risk or else disease onset may be predicated only by the final link (trigger effect) (Kuh et al 2003). Dong et al. (2004) provide a detailed example of this model in relationship to ischemic heart disease. They mapped the pathway from childhood adversities (including abuse, neglect and household dysfunction) to increased reactivity to stress leading to increased risk for negative affective states. Negative affective states (depression or anger) are now known to cause haemodynamic, hemostatic, immunologic and other endocrine changes leading to alterations in the platelet function and increased risk of coronary ischemia.

3. Life Course Approaches within the Psychiatric Epidemiological Research

Within psychiatric epidemiology, cohort designs have the greatest potential to shed light on causal mechanisms by which exposure to risk can lead to the development of mental disorders. They provide a framework for overcoming recall biases and allow the consideration of exposures and outcomes in a temporal context. Moreover, they

provide data amenable to life course analyses and are therefore the ideal ground for generating and testing aetiological models for mental health. The most prominent birth cohorts include the Dunedin Multidisciplinary Health and Development Study (DMHDS) (Silva, 1990), the British 1946 Birth Cohort (BBC) (Wadsworth, 1987), the National Child Development Study (NCDS) (Power and Elliott, 2006), the 1970 British Cohort Study (BCS) (Ferry et al., 2003), the Northern Finland 1966 Birth Cohort (NFBC) (Rantakallio, 1988), the Child Health and Development Study (CHDS) (Van den Berg et al., 1988) and the Christchurch Health and Development Study (ChrHDS) (Fergusson and Horwood, 2001). For these studies, 1,000 to 20,000 individuals from well defined-geographical areas were assessed from pregnancy or birth and were followed-up at regular intervals with low to moderate attrition rates. Follow-up periods have been of sufficient length so as to capture sufficient cases of schizophrenia, depression or anxiety disorders. Findings stemming from birth cohorts have substantially contributed to the field of translational epidemiologic research, a term used to describe the application of findings into innovative primary and secondary interventions and therefore into new clinical practices and public health policies (Weissman et al., 2011). Figure 1 summarizes some of the evidence identified and illustrates the notions of critical periods and accumulation of risk while assuming that the risk conferred by genetic factors is constant.

3.1 Critical Periods

Most of psychiatric epidemiology has focused on the notion of critical periods with main emphasis on the foetal and adolescent periods. Similarly to medical disorders, prenatal exposure to famine has been also shown to play a significant role for the development of mental disorders. Brown et al (2000) provide an early example of significant associations between exposures to prenatal famine during the second and third trimester and major affective disorder in adulthood. Exposures to the rubella (Brown et al., 2001) and the influenza virus (Brown et al., 2004) during pregnancy are strongly associated with adult schizophrenia; specifically, the risk for psychotic illness in adulthood may increase 7-fold, (95% CI 0.7-75.3) following exposure to the influenza

virus during the first trimester of gestation. In contrast, exposure to the same virus during the second or third trimester confers smaller risk [2nd trimester: 1.1 (95% CI 0.3-3.9); 3rd trimester: 1.1 (95% CI 0.5-2.6)].

Adolescence is also commonly considered a critical period because of documented evidence for brain maturation processes (Whitford et al., 2007) and hormonal changes (Sisk and Zehr, 2005). Cannabis use during adolescence is a frequently studied risk factor for the development of psychosis (Figure 1). Cannabis use at age 14-15 years appears to increase the risk of psychosis in adulthood by 4.50 (95% CI 1.11 to 18.21) while the risk for users at age 18 is substantially lower (1.65; 95% CI 0.65 to 4.18) (Arseneault et al., 2002) and is similar to that observed following cannabis use in early adulthood [1.68 (95% CI 0.37–7.51)] (Grech et al., 2005).

3.2 Accumulation of Risk

Relatively fewer studies have examined the accumulation of risk models with most recent examples focusing on the role of cannabis. In addition to influencing risk during critical periods, the effect of cannabis on the risk for psychosis increases further the greater and more prolonged the duration of exposure (Grech et al., 2005; Semple et al., 2005) (as illustrated in Figure 1). Furthermore, cannabis appears to act synergistically with other risk factors to increase and maintain the risk for psychosis (Cougnard et al., 2007; Houston et al., 2008; Harley et al., 2010). A typical example is provided by Harley et al (2010), who examined the interactions between childhood trauma and cannabis use with respect to the development of psychotic symptoms (Figure 1). In their study each risk factor independently increased the risk of psychotic symptoms. The individual risk conferred was 2.6 (95% CI 0.25–14.6) for childhood trauma and 1.9 (95% CI 0.04–16.5) for cannabis use. However, the interaction of childhood trauma and cannabis use increased the likelihood of psychotic symptoms by tenfold to 20.9 (95% CI 2.3–173.5).

In terms of chains of risk research in depression has yielded the most consistent findings to date. A common cascade of exposures leading to depression begins with maternal depression which increases the risk of family adversity (Murray et al., 1996) leading to increased reactivity to stress reflected in Hypothalamic-Pituitary Adrenal (HPA) axis dysregulation (Halligan et al., 2004). Increased stress reactivity increases the risk of negative affect during adverse life exposures and further disrupts the HPA axis. This has been associated with reduced hippocampal volume and prefrontal cortical activation which increase the risk of clinical depression (Palazidou, 2012).

Accumulation of risk and critical periods are not two mutually exclusive models. Shanahan and Hofer (2011) have recently described how such life course models could explain the interaction between genetic and social risk factors of disease. They posit that exposure to certain social risk factors during critical or sensitive periods may not only impact on biological structure or functions but may greatly influence subsequent social experiences forming a “chain of insults” and resulting in cumulative disadvantage.

The studies highlighted illustrate the potential of life course approach in disentangling the complex architecture of risk for psychiatric disorders and in providing a deeper understanding of how different life course models might complement each other. These theoretical models when paired with fast developing statistical techniques present new opportunities for the investigation of the mechanisms of conversion to psychopathology.

3.3 Traditional multivariate analyses vs. advanced statistical modeling techniques

A statistical model is formally defined as a set of probability distributions on the sample space (McCullagh, 2002), but can be simply conceptualized as the explanation of the relationships between variables using mathematical equations. To date, the most commonly used modelling approaches in psychiatric epidemiology have been linear and logistic regression or proportional hazard models. Yet, these models are limited when

employing a life time approach for two main reasons; first, they cannot estimate separate regression lines for each individual (i.e. they neglect important information on inter-individual variability) and second they rely on the assumption that the intercept and rate of change (slope) of additional explanatory variables are error free (Bollen and Curran, 2006).

These limitations can now be tackled by utilising different analytical tools that broadly fall under category of Structural Equation Modelling (SEM). These include but not restricted to Latent Growth Models (LGMs), Multivariate LGMs with or without Time In-varying Covariates (TICs) and Time Varying Covariates (TVCs), Autoregressive Latent Trajectory models (ALTs) (McArdle and Hamagami, 1992; Curran and Hussong, 2003; Bollen and Curran, 2004; Ludtke et al., 2008; MacKinnon, 2008; Rabe-Hesketh and Skrondal, 2008; Chavance et al., 2010). The main advantage of these models is that they provide the framework to overcome the implicit assumption of no unmeasured confounding within life course approaches. The central aim of psychiatric research on risk factors of mental disorders using life course approaches is the search for causative relationships between exposures and outcomes. Causal inference is best addressed using Randomized Control Trials (RCTs). Within the life course approach framework one of the main challenges for causal inferences has been to tackle the assumption of no additional confounding due to unmeasured factors (Gilman, 2007). Linear and non-parametric SEMs have now been used as alternative methods that allow researchers to make causal inferences in the presence of unmeasured confounders (Pearl, 2000; Hernan and Robins, 2006; Martens et al., 2006). Additionally, LGMs can identify the unique change in the variance of the slope and rate of growth of variables within and across individuals. This type of information would address questions concerning critical periods of exposure and accumulation of risk more precisely. Specifically, these models allow for a) detecting patterns of non-linear change, e.g. quadratic or cubic functions (LGMs); b) incorporating repeated measures of a covariate as a direct predictor of the repeated measures of a dependent variable in the presence of the growth process of

that dependent variable (Multivariate LGMs); c) expressing the repeated measures of a variable as a function of a set of parameters while implying that later observations are a direct function of earlier observations plus some time-specific error (ALTs).

As an example we can examine recent findings on cognitive functioning in patients with schizophrenia. The meta-analysis by Woodberry and colleagues (2008) suggested that cross-sectional designs can only demonstrate that patients have IQ deficit at different time points but are unable to address the persistent question of whether IQ declines within individuals with illness progression. In response Reichenberg et al (2010) modeled the cognitive trajectories prior to schizophrenia onset using latent growth curves by utilizing the DMHDS sample. This constitutes a sensitive approach in terms of identifying the unique variability in the growth rate of IQ at multiple measurement points with the potential to identify a) the temporal relationship between IQ decline and illness onset and b) non-linear trajectories of developmental deficits. Therefore, Reichenberg and colleagues were able to delineate the differences in the developmental course of various cognitive functions from childhood to early adolescence (Figure 2) and to identify the pre-morbid decline in executive function associated with schizophrenia. Similar approaches have been successfully applied in other areas of epidemiological research (e.g. Chen et al., 2007).

Despite the availability of longitudinal cohorts epidemiological psychiatric research to date presents with four key limitations. Firstly, examination of critical periods has been limited to narrow developmental windows (instead of taking a life course perspective) and to one or two risk factors (Ben-Shlomo and Kuh, 2002). Secondly, the few studies that have examined accumulation of risk models have been limited primarily by retrospective or cross-sectional data collection (Clemmons et al., 2007; Picken et al., 2010). Thirdly, even studies based on prospective data, have commonly focused on the association between a range of risk factors and outcome. Thus they account only for a relatively small proportion of the total variance and neglect to test for interactions

between risk factors. Moreover, the frequent use of composite indices obscures the temporal effects of risk factors and fails to distinguish between critical periods and accumulation of risk (Jaffee et al., 2002; Koenen et al., 2007). Fourthly, there is considerable lack of clarity between measures that constitute risk factors and measures that reflect health outcomes. For example, although cannabis use in adolescence is a risk factor for psychosis (Arseneault et al., 2002; Fergusson et al., 2003), substance abuse can also be considered an adverse diagnostic outcome (Fergusson et al., 1994; Fergusson et al., 1996; Koenen et al., 2009; Melchior et al., 2007; Woodward and Fergusson, 2001).

4. Directions for Future Research

There has been tremendous progress in our understanding of risk factors and their possible immediate and long-term effects, either independently or in combination. However, there is still much potential for further advancement. We have advocated the benefits of a systematic implementation of life-course models to epidemiological research in psychiatry. This is particularly timely given the recent wider availability of the necessary computational and statistical instruments required. Below we make specific suggestions with regards to the research areas to be prioritised.

A lifecourse approach could advance the field in at least five distinct directions. Firstly, by interrogating available data it would be possible to identify critical periods beyond the early years or life. An example could be exploring the possibility that in women perimenopausal estrogen decline (Seeman, 2010) may trigger a late “critical period” for the onset of schizophrenia between the ages of 45 to 50 years (Häfner, 2005). Secondly, the impact of risk factors may change in magnitude across the lifespan. This has been shown with regards to developmental trajectories for cognitive risk factors in schizophrenia (e.g. Kremen et al., 2008; Reichenberg, et al., 2010). Thirdly, Kendler et al. (2010) suggested that the effects of interactions of risk factors are of secondary importance to main effects and should be examined only if there is a strong theoretical

background. Therefore, modelling of interactions should proceed by testing the robustness of different theoretical assumptions with regards to the timing and conditions under which risk factors may influence disease onset. Fourthly, most studies to date have considered the effect of risk factors on a single outcome. Relatively less is known about the possibility of a particular risk factor increasing the probability for variable outcomes. Such a pluripotent effect of risk factors has been shown for family history of schizophrenia which increases the probability of multiple other adverse mental health outcomes (Dean et al., 2010). Focusing on the variability of outcome has the added advantage that it may lead to identification of protective factors against adverse mental health and will allow modelling future interventions not simply on risk minimisation but also enhancement of resilience. Fifthly, implicit in all current research is the notion that risk factors, particularly those in early life, are “embodied” or in other words, that they produce an irreversible biological changes which then influences adult health outcomes. The logical next step is to identify the relevant biological pathways as a means towards identification of causative mechanisms underlying disease expression. A recent example is provided by Lederbogen et al (2011) with regards to urbanicity, a factor known to increase the incidence and prevalence of a range of mental disorders. The authors found that urbanicity was associated with increased activation in the amygdala and anterior cingulate cortex during cognitive tasks when they were performed under conditions of social stress (Lederbogen et al., 2011).

In sum, the evidence we have presented points to new avenues in study design and data analysis. It is our view that there are three priority areas, namely a) modelling and testing pathways showing how risk factors might relate to critical periods of biological development, b) assessing the cumulative effect following prolonged exposure or the potential clustering with other factors and c) identifying chains of risk as yet not fully described.

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Fig. 1 Critical periods of risk exposure and cumulative interactions of risk factors for psychotic illness: an illustrative example of the most prominent findings

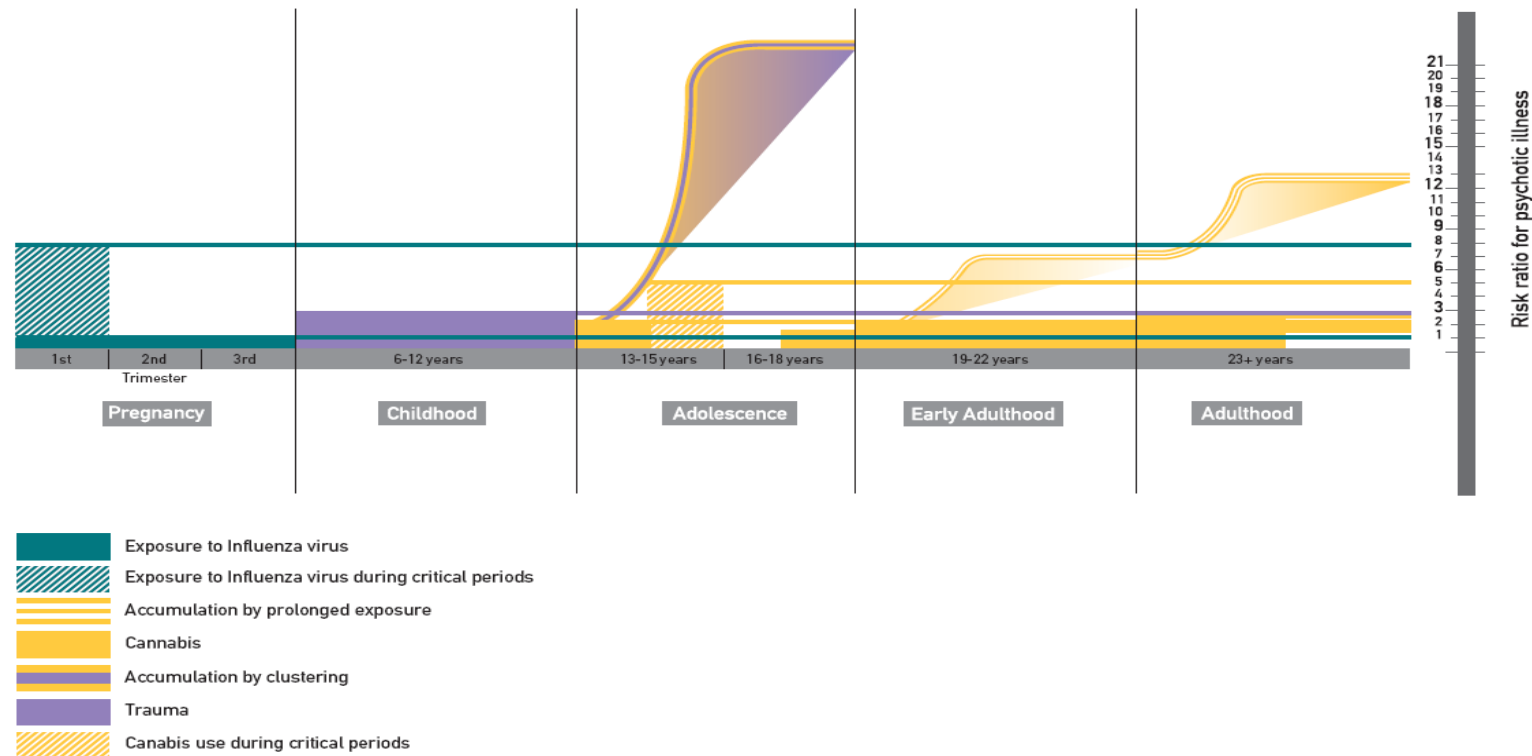
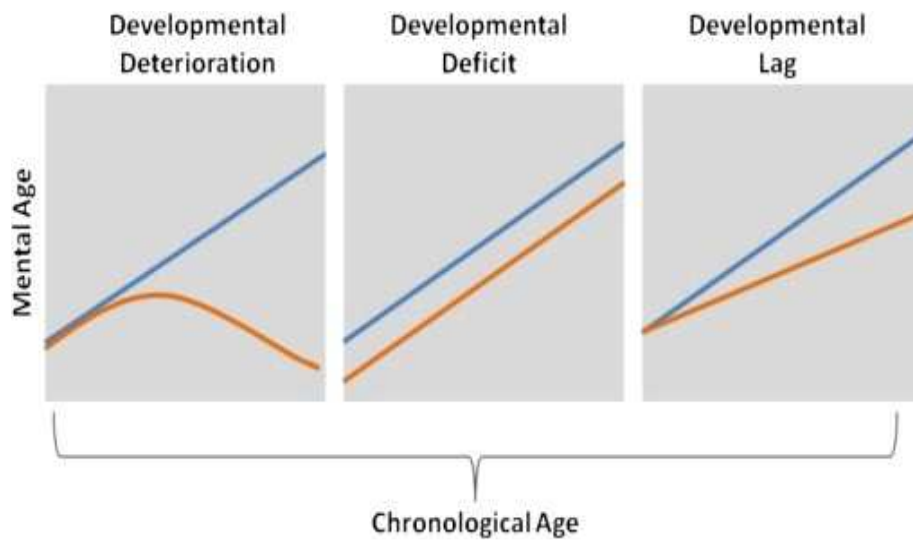


Fig 2. Differences in the developmental course of cognitive functions from childhood to early adolescence with schizophrenia: an illustrative example



2 Life course approach for bipolar disorder

2.1 Introduction

In this chapter the concept of Bipolar Disorder (BD) is introduced by examining its associated clinical features. Subsequently, the importance of disentangling the mechanisms leading to BD are highlighted by reviewing studies on the increased personal and societal burden associated with BD. Moreover, the evidence on prevalence rates for BD in the general population and in youths as well as the comorbidities with other psychiatric disorders is reviewed. The chapter concludes by emphasizing the importance of life course approaches for the study of BD in relation to the identification of a valid prodromal phase and conversion to BD. The objectives and hypotheses of each study are formulated in the corresponding Chapters 4-6.

2.1.1 Clinical Features

BD is characterized by profound and pathological changes in mood. It presents with recurrent episodes of depression interspersed with periods of mania and is associated with significant psychosocial morbidity and mortality (Baldessarini and Tondo, 2003). In its classic form, or BD type 1 (BD-I), the illness is defined by the presence of at least one manic episode (World Health Organisation(WHO), 1993; APA, 1994). The spectrum of BD disorders also includes BD type II (BD-II), and cyclothymia. In both, manic symptoms are milder and of shorter duration. In contrast, depressive symptoms are common across all subtypes of BD and overlap with the presentation of unipolar or major depressive disorder (in which the patient never has mania or hypomania).

2.1.2 Personal and Societal Burden

BD is one of the leading causes of disability worldwide (WHO, 2008). This also applies to Europe in general (Fajutrao et al. 2009). In the UK the direct (e.g. the unit resource costs) and indirect costs (e.g. excess unemployment, absenteeism and suicide)

attributable to BD are almost 2 billion pounds per year (Das Gupta et al., 2002). These costs remain high as in 2009/2010 the annual cost of BD to the National Health Service (NHS) reached £342 million (Young et al., 2011). Estimates of the total costs of BD in the USA may be even higher exceeding 45.2 billion dollars (Wyatt & Henter, 1995).

The negative impact of BD is accentuated by its early onset with the majority of patients presenting between 16-35 years of age (Perlis et al., 2004; Berk et al., 2007a; Merikangas et al., 2011). Additionally suicide is a major concern as standardized mortality ratios for suicide in BD range between 12.3 and 22.4 (Wunderlich et al., 1998; Ósby et al., 2001). BD can also lead to profound disruptions in work and social functioning, including high unemployment rates and relationship breakdowns (Mitchell & Malhi, 2004; Morgan et al., 2005; Kessler et al., 2006; Ruggero et al., 2007; Zimmerman et al., 2010).

2.2 Prevalence of BD

2.2.1 Lifetime Prevalence of BD

The reported prevalence rates vary greatly. Akiskal et al. (2000) summarized important methodological factors which can at least partially account for this variability. These include the breadth of the criteria used to define BD, the type of diagnostic instruments, the experience and background of the interviewer (lay vs. clinical), the population studied, sample size, the number of observations (single vs. repeated), informant (interview of patients vs. relatives) and the timing of the interview.

Studies that use a narrow definition for syndromal BD-I report low lifetime prevalence rates. Kessler et al. (1994) reported a rate of 1.6% in a representative US national sample of 8,098 participating in the National Comorbidity Survey (NCS) and Regier et al. (1988) reported 1.2% lifetime prevalence in 18,571 subjects participating in the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) program.

Higher rates have been reported when the definition of BD was broadened to include bipolar spectrum disorders (i.e. brief hypomania and cyclothymia) and subthreshold hypomania lasting less than 4 days. Angst et al. (1998) applied these criteria to the Zurich cohort and found a cumulative prevalence rate over four interviews of 5.5 % (hypo)mania for participants up to age 35 years. A similar rate of 5.1 % for bipolar spectrum disorders was reported in a Hungarian adult population sample (18-64 years) (Szádóczy et al., 1998).

Recent epidemiological studies have commonly used the Composite International Diagnostic Interview (CIDI), a structured lay-administered diagnostic interview, to diagnose BD based on DSM-IV and ICD-10 criteria (Kessler et al. 2005; Merikangas et al. 2007) and to estimate the prevalence of broader definitions of BD that include recurrent hypomania without a major depressive episode or subthreshold hypomania (Merikangas et al., 2007). In a nationally representative sample of 9,282 US adult members of the National Comorbidity Survey Replication (NCS-R) the lifetime prevalence rate for syndromal BD was reported to be 2.6% with a 12-month prevalence of 2.6% in 2005 (Kessler et al. 2005) and 1.4% in 2007 (Merikangas et al., 2007). Lifetime prevalence of BD was increased to 4.5% when considering subthreshold expressions (Merikangas et al., 2007).

2.2.2. Prevalence of BD in Youth

Typical lifetime prevalence rates of BD in younger populations range from 1.0% (Lewinsohn et al., 2000) to 1.8% (Wittchen et al., 1998) and 6 to 12 month prevalence range from 0.4% (Verhulst et al., 1997) to 2.5% (Benjet et al., 2009). A recent meta-analysis of 12 studies examining the prevalence of BD in community epidemiological samples of youths aged 7 and 21 years reported an overall rate of 1.8% (95%CI 1.1%-3.0%) (Van Meter et al., 2011). The rates of bipolar spectrum disorders in the studies included in this meta-analysis ranged from 0.0% (Lynch et al., 2006) to 6.3% (Kessler et al., 2009).

The most recent findings stem from the NCSR-Adolescent Supplement (NCSR-A) (Merikangas et al., 2010; Kessler et al., 2012). The sample of the NCS-A included 6,483 adolescents aged between 13 and 17 years. The reported lifetime prevalence rate for BD was 2.9% (95%CI 2.3%-3.5%) (Merikangas et al., 2010). For the 12-month and 30- day prevalence periods the rates were 2.1% (95% CI 1.7%-2.5%) and 0.7% (95% CI 0.5%-0.9%) respectively (Kessler et al., 2012).

2.3 Bipolar Disorder Across the Life-Span

2.3.1 Age-Dependent Manifestations of BD

BD characteristically begins in adolescence or early adulthood with the modal age of onset between 16 and 20 years (Roy-Byrne et al., 2007; Mesman et al., 2013) that does not differ between sexes (Kawa et al., 2005). While BD can be diagnosed in children and adolescents (early onset BD) (Axelson et al., 2006; Birmaher et al., 2006a) the symptoms may be atypical with mixed and dysphoric features being more prominent than in adults (Birmaher et al., 2006b; Berk et al., 2007b). Cases of early onset BD are often comorbid with other common childhood disorders (Geller et al., 2002; Youngstrom et al., 2005; Carlson and Meyer, 2006).

Therefore, the task of diagnosing youths with BD is challenging. Berk et al. (2007b) outlined a number of reasons that contribute to the complexity of ascertaining BD in younger patients. The main ones included a) patients denial or misattribution of symptoms of mania; b) mild mania can be pleasant and may not necessarily be considered as symptomatic of an illness; c) phenomenological overlap with agitated depression; d) disruptive symptoms and irritability being interpreted as an abnormal personality; e) frequent misdiagnosis of BD as Attention Deficit Hyperactivity Disorder (ADHD); f) presence of multiple comorbid conditions; and g) psychotic symptoms being seen as diagnostic of schizophrenia and not mania.

In addressing these issues several studies have tried to define the symptomatic profile and variation of BD from 5 years of age onwards using factor analytic techniques (Youngstrom 2002; Frazier 2007; Papolos 2007; Youngstrom 2008; Topor 2013). The number of factors extracted ranged from 1 (Youngstrom et al. 2002) to 10 (Papolos et al., 2007). The difference in the number of factors can be accounted for by the different instruments used, potential age differences in the presentation of manic symptoms and the age of onset relative to the age of assessment.

Two studies, Youngstrom et al. (2002) and Frazier et al., (2007), have attempted to address the issue of age differences in the presentation of manic symptoms by comparing the factor structure of manic symptomatology in children to that of adolescents. Both studies report that a single factor-solution described both age groups suggesting a similar manifestation of bipolar symptomatology in children and adolescents.

Additionally, one study (Topor et al., 2013) has examined the factor structure of manic symptomatology relative to the age of symptoms onset and current age. In this study, 347 youths with childhood or adolescence onset BD were assessed using the Schedule of Affective Disorders and Schizophrenia for School-Age Children (K-SADS) Mania Rating Scale (MRS). The results suggest that a 2-factor structure, termed “activated/pleasure seeking” and “labile/disorganized/psychotic” fitted the data best for children with childhood onset BD and for adolescents with adolescence-onset BD. Symptoms for adolescents with childhood onset BD were best described by a single factor encompassing both “activated/pleasure-seeking” and “disorganized” symptoms but not labile behavior. The authors suggest that the reduced factor structure observed in this group of adolescents might be an artifact of recall errors resulting from longer time period between symptom onset and assessment (Topor et al., 2013). Although plausible, these findings are yet to be expanded in longitudinal settings in order to assess the temporal stability of manic manifestations. In **Chapter 4 (Child Behavior Checklist- Mania Scale (CBCL-MS): Development and validation of a population-based**

scale for bipolar disorder) I address this issue by examining the underlying (i.e. latent) structure of manic symptoms from childhood (11 years) to adolescence (16 years) using a newly developed scale, the CBCL-MS.

2.3.2 Illness Severity in relation to Age of Onset

Perlis et al. (2009) suggested that early identification and diagnosis may allow for earlier treatment that may improve long-term outcomes. However, the delay between onset and diagnosis of BD is typically between 5-10 years (Lish et al., 1994; Baethge et al., 2003; Hirschfeld et al 2003; Berk et al, 2007b).

Early onset of BD is a predictor of worse clinical outcomes compared to adult onset cases as it is associated with higher number of comorbidities, more suicide attempts and increased illness severity in terms of number and duration of episodes (McElroy et al., 2001; Carlson et al., 2002; Perlis et al., 2004; Larsson et al., 2010; Post et al., 2010). In a key study using data from seven international centers, Baldessarini et al. (2012) not only confirmed that early onset BD was associated with worse clinical and but also demonstrated greater impairment in functional outcomes including employment, living conditions, marital status, and education.

However, the effect of early onset on outcome may be mediated by factors not directly related to increased illness severity such as family adversity and cumulative psychosocial disadvantage caused by the early disruption in education and social role attainment (Levy et al., 2012). In chapter 5 and 6 (**Chapter 5. Alarm Symptoms in the early diagnosis of bipolar disorder: a population based cohort study; Chapter 6. Trajectories to Bipolar Disorder from childhood to adulthood**), I examine the effect of multiple sociocognitive and familial risk factors on trajectories into BD. This information can shed light on mechanisms leading to overt disease expression and has the potential to identify points for primary and secondary intervention.

2.3.3 Psychiatric Comorbidities

Adult patients with BD present with high rates of comorbid Axis I disorders particularly substance use, anxiety disorders (Chen et al., 1995a; Chen et al., 1995b; Kessler et al., 1996; Szadoszky et al., 1998) and eating disorders (Kruger et al., 1996; McElroy et al., 2001). McElroy et al. (2001) examined psychiatric comorbidities in 288 adult patients with BD and found that 42% had comorbid anxiety and substance use disorders and 5% had eating disorders. In the NCSR the comorbidity rates were 5.7% for anxiety disorders and 39.1% for substance use disorders (Merikangas et al., 2007). Generally, Axis I psychiatric comorbidities are associated with earlier age of onset of BD, higher rates of suicidality, poorer overall outcome and less favorable response to lithium (McElroy, 2001; Post et al., 2010).

High rates of comorbid psychiatric disorders have also been reported in early onset BD although the rates vary depending on sample selection (clinical versus community samples), method of diagnostic ascertainment (routine clinical interviews, structured diagnostic interviews, type of diagnostic instrument, availability of informants, clinical experience of the interviewer) and diagnostic classification system (Pavuluri et al., 2005). For example, because disorders are hierarchically classified in the DSM-IV a diagnosis of Oppositional Defiant Disorder (ODD) cannot be made in the presence of BD. Current estimates suggest that in early onset BD comorbidity rates are between 46.4% and 75% for ODD, 5.6% and 37% for conduct disorder, 12.5% and 56% for anxiety disorders, and 0% and 40% for substance abuse disorders (Pavuluri et al., 2005). However, the most common comorbid condition is ADHD; up to 85% of youth with BD may also have ADHD while up to 25% of those with ADHD may also suffer from BD (Singh et al. 2006). The type of comorbidities depends largely on the age of onset; Findling et al. (2001) and Wilens et al. (2004) have shown that young children with BD are more likely to have comorbid ADHD while older adolescents are more likely to have comorbid substance abuse disorders.

The high rates of comorbidity may be explained by shared genetic vulnerability as has been suggested for substance use (Lin et al., 2006), anxiety disorders (Erhard et al., 2007; Goes et al., 2012) and ADHD (Faraone et al., 1997; Neslihan Inal-Eiroglu et al., 2008). BD and ADHD may also share neurobiological correlates (Zepf, 2009; Passarotti et al., 2010a; Passarotti et al., 2010b; Skirrow et al., 2012).

2.3.4 Differential Diagnosis of BD

In adult patients the main difficulty lies in the differential diagnoses of BD from major depressive disorder (MDD). This is because depressive symptoms tend to dominate the clinical presentation of BD both at onset and during the long-term course of the disorder (Perugi et al., 2000; Judd et al., 2002). Additionally, BD is associated with high rates (between 60-80%) of psychotic symptoms during mood episodes; especially in younger patients this may result in difficulties in differentiating BD from schizophrenia (Keck et al., 2003; Coryell et al., 2001).

In youth with BD the main challenge is the differentiation of BD from other disorder of disruptive behaviour, particularly ADHD. Two main distinguishing features have been proposed. Geller et al. (2002) emphasized the importance of elevated mood, grandiosity, flight of ideas, hypersexuality and decreased need for sleep for a diagnosis of mania. Others consider episodicity as important in differentiating between BD from other disruptive disorders such as ADHD (Carlson, 1998; Asherson et al., 2007; Leibenluft and Rich, 2008; Youngstrom et al., 2010). Some have challenged this based on findings that children and adolescents with BD tend to experience more chronic symptoms and clear episodes may not be easy to identify (Biederman et al., 2004).

Psychotic symptoms, particularly mood-incongruent delusions and hallucinations and thought disorder can lead to misdiagnosing BD as schizophrenia in as many as 50% of early onset BD cases (Carlson, 1990; Werry et al., 1991). Finally, the activation and inhibition resulting from substance abuse (Wilens et al., 1999) as well as the irritability

and emotional lability associated with internalising and externalising conditions, including ODD, conduct, anxiety, depressive and borderline personality disorders (Leibenluft et al., 2003; Cumyn et al., 2009; Stringaris and Goodman, 2009; Skirrow et al., 2012) can also be mistaken for mania. In Chapter 4 (**Child Behavior Checklist- Mania Scale (CBCL-MS): Development and validation of a population-based scale for bipolar disorder**), I examine the ability of behavioural assessments of different symptom dimensions of BD in youths to distinguish between BD and other diagnostic categories, particularly MDD, general anxiety disorder and ADHD.

2.3.5 The concept of prodrome in bipolar Disorder

Results from retrospective studies suggest that about a third of patients report difficulties in mood regulation before the full blown onset of BD (Lish et al, 1994; Egeland et al, 2003; Hirschfeld et al, 2003; Berk et al, 2007a; Corell et al, 2007; Mantere et al., 2008). This evidence suggests that prior to their first manic episode patients may experience prodromal symptoms for an average of 2 years, most commonly mood lability, excitability, low energy and mood and insomnia with variable impairment in functional roles (Egeland et al, 2003; Shaw et al, 2005; Corell et al, 2007; Mantere et al., 2008; Skjelstad et al., 2010). Although these studies provide support for the presence of a prodrome in BD, the evidence derives mostly from affected offspring of BD patients (Hillegers et al. 2005; Duffy et al, 2007) and from patients with childhood onset BD (Correll et al, 2007; Birmaher et al, 2009; Birmaher 2010; Luby and Navsaria 2010). This raises concerns about generalisability since approximately half of BD patients do not have a positive family history of the disorder (Tijssen et al, 2010a; Baldessarini et al., 2012) and onset in childhood is rare and therefore atypical (Larsson et al 2010).

Additionally, the sensitivity and specificity of these putative prodromal symptoms has yet to be determined. This issue is of particular importance since putative signs of incipient BD require differentiation from normal, self-limiting mood fluctuations that

are common in adolescence and young adulthood (Tijssen et al, 2010b), a period that coincides with the peak incidence years for BD (Perlis et al, 2004; Berk et al, 2007a).

Finally, all studies in this area have been symptom based, in other words they have focused on score values for one or more dimensions of psychopathology. It is becoming increasingly apparent that symptom-based approaches are not helpful as symptom dimensions are not pathognomonic (Krabbendam et al, 2004). Therefore the success of diagnostic and intervention strategies is based on our ability to move to person-centred approaches and define the characteristics of groups of individuals at risk for BD in order to characterise their mental health needs and help seeking behaviour for use in future strategies for early identification and prevention. In Chapter 6 (**Trajectories to Bipolar Disorder from childhood to adulthood**) I use a person centered approach within a longitudinal cohort study design to identify qualitative differences and transition rates of prodromal phases to clinically meaningful BD.

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3 Study Population

3.1 Introduction

The methodological approach followed in each of the studies comprising Chapters 4-6 (**Chapter 4. Child Behavior Checklist- Mania Scale (CBCL-MS): Development and validation of a population-based scale for bipolar disorder; Chapter 5. Alarm Symptoms in the early diagnosis of bipolar disorder: a population based cohort study and Chapter 6. Trajectories to Bipolar Disorder from childhood to adulthood**) are described in the corresponding chapters. The focus of this chapter is to introduce and describe the Tracking Individuals Lives Survey (TRAILS), a prospective cohort study which commenced in 2001 in Groningen, Holland and provided the data used to address the objectives of this thesis. Therefore, this chapter will commence by providing an overview of the organization of TRAILS and a description of the relevant ethical approval obtained. Next, the analytic cohort will be described and the chapter will conclude by a description of the instruments used in the studies.

3.2 Overview of the Tracking Individuals Lives Survey (TRAILS)

TRAILS (www.trails.nl/en/) is an ongoing prospective multidisciplinary cohort study which commenced in 2001 and acquired biennial assessments of sociocognitive, familial and psychological characteristics of 2,230 youngsters. The first assessment wave (T1) took place during 2000-2001, the second (T2) during 2003-2004, the third during 2005-2007 (T3) and the fourth during 2008-2010 (T4). Currently, the fifth wave (T5) is being finalized. Data from T5 were not included in the analyses of the studies presented in this thesis as it has not yet been completed.

The primary aim of TRAILS was to study the mental, social and physical development of children throughout their adolescence and early adulthood. By September 2012, more

than 170 publications using data collected by TRAILS had been published in international peer-reviewed journals. TRAILS, therefore, takes aim to disseminate gained knowledge among international professional colleagues, professionals in mental health and education, policy makers and other stakeholders.

The data collected by TRAILS cover a broad range of domains including a) mental health/general adjustment, b) physical health and development, c) family characteristics, d) personality and social development, e) cognitive data f) biological data and others. These were obtained from multiple sources including self-reports, parents, siblings, teachers and peers.

TRAILS is managed by the University Medical Centre of Groningen (UMCG) and the Erasmus Medical Center of Rotterdam. Other participating universities include the Radboud University Nijmegen Medical Centre and Utrecht University. The principle investigators are Prof. A.J. Oldehinkel of the Department of Psychiatry of the University Medical Center Groningen, and Prof. F.C. Verhulst of the Department of Child and Adolescent Psychiatry of the Erasmus University Medical Center Rotterdam. The research group of TRAILS consists of a multidisciplinary team of members of various departments, including (child and adolescent) psychiatry, epidemiology, biostatistics, social sciences, health sciences, kinesiology, pediatrics and respiratory disease across several universities throughout The Netherlands. Other key members of TRAILS include the additional head investigators Dr. C.A. (Catharina) Hartman and Prof. dr. J. (Hans) Ormel of the University Center for Psychiatry, UMCG.

TRAILS is financially supported by grants from The Dutch Organisation for Health Research and Development (ZonMw), The Dutch Organization for Scientific Research and the Department of Justice. Additional grants have been received by Sophia Stichting of the Erasmus Medical Center (WODC), the European Science Foundation (EuroSTRESS project FP-006), the Biobanking and Biomolecular Resources Research

Infrastructure BBMRI-NL (CP 32), the participating universities, and the Accare Center for Child and Adolescent Psychiatry.

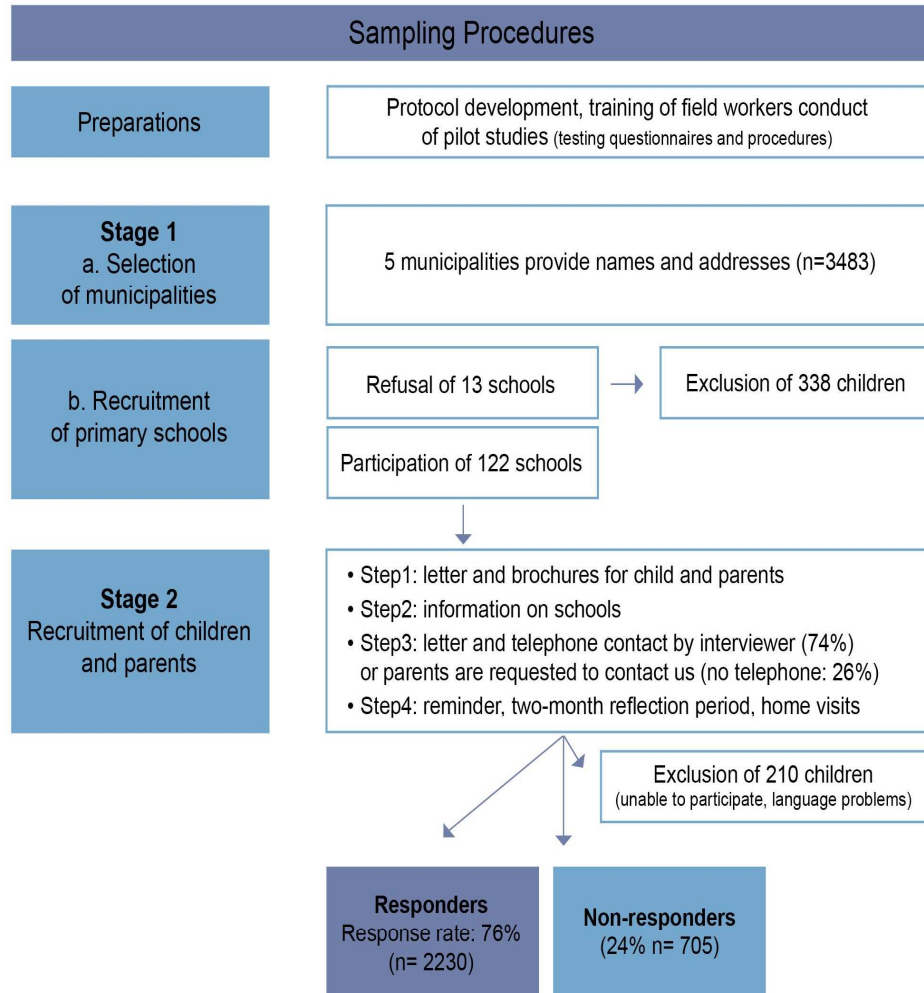
3.3 Ethics

TRAILS was approved by the national ethical committee 'Centrale Commissie Mensgebonden Onderzoek' and the Dutch Central Committee on Research Involving Human Subjects (CCMO). Permission for me to use anonymised data from the survey was granted by the study management committee. All data were anonymised according to the UMCG research code guidelines (<http://www.rug.nl/umcg/research/general/research-code>) and the research office TNS NIPO [<http://www.tns-nipo.com/>] protocols.

3.4 The analytic cohort

The sampling procedure followed by TRAILS is described in three studies (de Winter et al., 2005; Huisman, et al., 2008; Ormel et al., 2012) and is summarized in Figure 3.1. Briefly, it consisted of two stages. During the first one, five municipalities in the North of Netherlands were contacted to obtain demographic details of all children born between 1 October 1989 and 30 September 1991; subsequently, 135 schools were identified and invited to participate in the study (N=3,483). 13 schools (338 children) refused to participate. During the second sampling stage, the parents of the identified children were informed about the nature and objectives of the study and were invited to participate. Of the 3,145, 210 were unable to participate for various reasons including severe mental retardation and non-Dutch speaking parents or parent surrogates, thus resulting in a baseline sample of 2,230 participants with a mean age of 11.1 years (M=11.09, SD= 0.56).

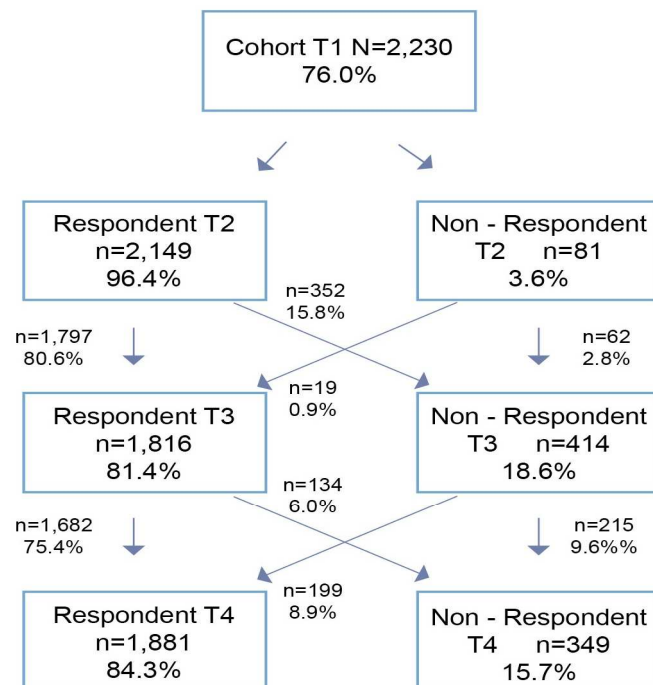
Figure 3.1 Sampling Procedures of TRAILS



De Winter et al., 2005

The attrition rate during the subsequent waves of assessment has remained low and is summarized in Figure 3.2. 2,149 subjects participated in the second wave (96% of baseline sample; mean age $M=13.55$, $SD=0.54$), 1,816 in the third wave of assessment (81.4% of baseline sample; mean age $M=16.27$, $SD=0.73$) and 1,881 in the fourth wave of assessment (84.3% of baseline sample; mean age $M=19.08$, $SD=0.60$). Attrition at follow-ups was slightly higher in males and participants of nonwestern ethnicity, as well as in participants with divorced parents, low socioeconomic status and low IQ and academic achievement. Sexes are equally represented within the sample; specifically, the percentage of females was 50.8%, 51.00%, 52.3% and 54.6% for the four waves of data collection, respectively. The fifth wave of assessment remains ongoing and is expected to finish by the end of 2013.

Figure 3.2 Attrition Rates in TRAILS



3.5 Instruments

3.5.1 Outcome Measures

3.5.1.1 The World Health Organization (WHO) Composite International Diagnostic Interview (CIDI)

TRAILS investigators used the WHO-CIDI version 3.0 [Computer Assisted Interview (CAPI) version 20]] (<http://www.hcp.med.harvard.edu/wmhcdi/>) to ascertain lifetime psychiatric diagnoses based on ICD-10 and DSM-IV criteria during the fourth assessment wave (T4). The WHO-CIDI is a comprehensive, fully structured interview designed to be used by lay interviewers for the assessment of mental disorders as defined by the ICD-10 and DSM-IV diagnostic criteria and it allows investigators to measure the prevalence, severity, and burden of mental disorders as well as assess service use, the use of medications in treating these disorders and the barriers to treatment. The diagnostic section of the interview is based on the World Health Organization's Composite International Diagnostic Interview (WHO CIDI, 1990).

Wittchen (1994) in a review of studies assessing the reliability and validity of the CIDI reports that test retest agreement ranged from 81% (persistent pain disorder) to 97% (panic disorder) and interrater kappa coefficient from .67 (somatization) to .87 (major depression). For Bipolar Disorder (BD)-I, the WHO-CIDI has high test-retest reliability (87%) as well as excellent concordance rates (AUC=.99) with blindly administered clinical re-interviews using the non-patient version of the Structured Clinical Interview for DSM-IV (SCID) (Haro et al., 2006; Kessler et al., 2006). Additionally, excellent concordance rates with the DSM-IV (SCID) disorders have been reported for lifetime bipolar spectrum disorders (BDII and Hypomania) (Kessler et al., 2006).

3.5.1.2 CBCL

TRAILS participants were administered the Child Behaviour Checklist (CBCL) 6-18 (Achenbach & Rescorla, 2001), which is a revision of the CBCL 4-18 (T.M. Achenbach, 1991; T. M. Achenbach & Edelbrock, 1983) at ages 11, 13 and 16 (T1, T2 and T3). The

CBCL 6-18 is a parent- or parent surrogate- report checklist of child behaviour problems including various aspects of psychopathology in childhood and adolescence occurring during a specified period of time (e.g. the last 6 months) consisting of 118 items scored from 0 to 2 (0= not true, 1= somewhat or sometimes true, and 2= very true or often true) on the basis of the preceding 6 months (T.M. Achenbach, 1991). According to the results of factor analyses, scores can be summarized in eight syndrome scales or two broad groupings of syndromes which provide clinically useful associations with different diagnostic groups (Edelbrock & Costello, 1988; Eiraldi, Power, Karustis, & Goldstein, 2000; Kasius, Ferdinand, van den Berg, & Verhulst, 1997); these include a) 'Internalising Behaviours' encompassing the 'Withdrawn', 'Somatic Complaints' and 'Anxious/Depressed' scales; and b) Externalising Behaviours encompassing the 'Delinquent Behaviour' and 'Aggressive Behaviour' scales. The remaining scales include 'Social Problems', 'Thought Problems' and 'Attention Problems'. Items that are not accurately classified in any of these scales are summarized under 'Other Problems'.

Besides scoring profiles reflecting patterns of co-occurring problems, CBCL is an assessment instrument which can view children's problems from the perspectives of formal diagnostic systems, e.g. the DSM-IV. (T. M. Achenbach & Rescorla, 2001). Achenbach et al. (2001) have grouped items into the following DSM-oriented scales: Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Conduct Problems and Oppositional/Defiant Problems. In contrast to the factor analytic methods used to develop the Syndrom Scales, the DSM oriented scales were constructed through agreement in experts' ratings of the preexisting items' consistency with DSM-IV diagnostic criteria. These six scales present with high test-retest reliability and their Cronbach's alpha range from .71 for the Somatic Problems items to .89 for the Conduct Problems items (Nakamura, Ebesutani, Bernstein, & Chorpita, 2009). These instruments provide highly efficient ways to screen for several disorders including ADHD (Derks, et al., 2006), major depressive disorder and dysthymia (Ferdinand, 2008).

The DSM-oriented scales of the CBCL have also been cross-validated by a Semi-structured Clinical Interview for Children and Adolescents (SCICA)(McConaughy & Achenbach, 2001). Compared to a national sample of children rated by their teachers, clinically meaningful thresholds for a deviation from age-and sex-matched healthy children are standardized T scores ranging from 65 (93rd Percentile) to 69 (97th Percentile) which are considered to be in the borderline clinical range; T scores > 70 represent the clinical range (T. M. Achenbach & Rescorla, 2001).

The CBCL has been translated in over 90 languages including Dutch. In a study on 2,339 Dutch youths aged 4 to 18 years, results of factor analyses suggested that the syndrome scales were very similar in item composition to the ones derived originally by Achenbach (1991). Additionally, cross-national correlations ranged from .82 for the Social Problems syndrome to .99 for the Somatic Complaints and Anxious/Depressed syndromes. In the TRAILS sample items of the CBCL had moderate to high internal consistency at all three assessment waves. Specifically, Cronbach's alpha values ranged from 0.64 to 0.84, from 0.64 to 0.82, and from 0.65 to 0.82 for the DSM-oriented scales at T1, T2 and T3 respectively.

3.5.2 Additional Measures

3.5.2.1 Family Psychiatric Morbidity

At T1, family psychiatric morbidity was assessed using the TRAILS Family History Interview which includes parental self-reports of a lifetime history of psychiatric disorders. For this interview, parents were presented with a description of the main DSM-IV characteristics of each disorder, followed by a series of questions assessing lifetime occurrence, the impact of the symptoms, the professional treatment received and medication use when applicable. Parents were then assigned one of the following categories: 0= (probably) never had an episode, 1= (probably) yes, or 2= yes and treatment and/or medication. A single indicator of familial psychopathology was then

constructed as the pattern of associations between parental disorders and offspring psychopathology was similar for fathers and mothers despite the low correlation between maternal and paternal rates of occurrence of disorders (<0.20).

In total, 42% of children had at least one parent with a psychiatric disorder. The rates of reported paternal and maternal history of mental disorders in the TRAILS dataset were as follows: bipolar disorder (3.5% and 5.8%), major depressive disorder (16% and 27%), any anxiety disorder (5.3% and 15.1%), schizophrenia and spectrum disorders (1.9% and 2.1%) and substance abuse (including drugs and alcohol) (6.4% and 2.1%). With the exception of major depressive disorder these prevalence rates compare to lifetime prevalence rates reported in other Dutch longitudinal cohort studies, e.g. the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl et al., 1998).

3.5.2.2 Socioeconomic Status

Socioeconomic status (SES) at age 11 (T1) was measured using a composite index of five indicators: maternal and paternal education, family income and maternal and paternal occupation assessed by the International Standard Classification of Occupation (Ganzeboom & Treiman, 1996). A composite index of SES was constructed by averaging the five indicators upon standardization. This index captured 61.2% of the variance in the five items and presented with high internal consistency (Cronbach's $\alpha=0.84$). Missing values in cases such as single-parent families were accounted for in the averaging of the standardized items. Overall, 48.6% of TRAILS participants had middle SES, followed by 24.8% and 24.7% with low and high SES respectively.

3.5.2.3 Family Functioning

Family functioning at age 11 (T1) was measured using the General Functioning Subscale of the McMaster Family Assessment Device (FAD-GFS) (Epstein et al., 1983). The FAD-GFS is a 12-item scale designed to be completed by family members and assesses overall family functioning. Each item is rated from 1 (strongly agree) to 4 (strongly disagree); a

total score is then calculated from the valid summed item scores and divided by 12 with scores of 2 or above indicating problematic family functioning.

The FAD-GFS assesses six dimensions of family functioning; communications, problem solving, affective responsiveness, affective involvement, roles and behaviour control. In the TRAILS sample the scale presented with high internal consistency (Cronbach's $\alpha=0.84$).

3.5.2.4 Cognition

An estimate of intellectual ability at age 11 (T1) was obtained following standardized administration of the Vocabulary and the Block Design subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974). These two subtests were used as a proxy IQ score as they correlate highly with scores on the full test ($r=0.90$) (Sattler, 1982). A composite measure was calculated from the two subtests using the age-normalized standard scores. The IQ scores of the sample ranged from 45 to 149 and had a mean value of 97 ($M=97.19$, $SD=15.00$).

3.6 Missing Data

Missing data have been kept low for most variables included in the analyses. For mental health dimensions and CBCL data the percentage of missing data ranged between 6% - 31% and 8%-22% respectively. Two per cent of the data were missing for SES, and 2-3% were missing for lifetime parental psychopathology. For data that could be assumed to be Missing At Random (MAR) or Completely At Random (MCAR) we used listwise deletion for cross-sectional assessments. For the structural equation models fitted using MPlus 6.0 and 7.0 (www.statmodel.com) in Chapters 5 and 6, I used the full information maximum likelihood (FIML) estimation approach, which has been shown to produce unbiased parameter estimates and standard errors under the MAR and MCAR assumptions for data missing due to attrition. Where appropriate I performed multiple

imputations to minimize loss of statistical power and risk of bias using the SPSS IBM SPSS Statistics, Version 20 (www.spss.com).

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4 Child Behavior Checklist - Mania Scale (CBCL-MS): Development and evaluation of a population-based screening scale for bipolar disorder

Papachristou E, Ormel J, Oldehinkel AJ, Kyriakopoulos M, Reinares M, Reichenberg A, Frangou S. (2013). Child Behavior Checklist - Mania Scale (CBCL-MS): Development and validation of a population-based screening scale for bipolar disorder. *PLoS ONE* (in press)

**Title: Child Behavior Checklist - Mania Scale (CBCL-MS): Development and evaluation
of a population-based screening scale for bipolar disorder**

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Abstract

Context: Early identification of Bipolar Disorder (BD) remains poor despite the high levels of disability associated with the disorder.

Objective: We developed and evaluated a new DSM orientated scale for the identification of young people at risk for BD based on the Child Behavior Checklist (CBCL) and compared its performance against the CBCL-Pediatric Bipolar Disorder (CBCL-PBD) and the CBCL-Externalizing Scale, the two most widely used scales.

Methods: The new scale, CBCL-Mania Scale (CBCL-MS), comprises 19 CBCL items that directly correspond to operational criteria for mania. We tested the reliability, longitudinal stability and diagnostic accuracy of the CBCL-MS on data from the TRacking Adolescents' Individual Lives Survey (TRAILS), a prospective epidemiological cohort study of 2230 Dutch youths assessed with the CBCL at ages 11, 13 and 16. At age 19 lifetime psychiatric diagnoses were ascertained with the Composite International Diagnostic Interview. We compared the predictive ability of the CBCL-MS against the CBCL-Externalising Scale and the CBCL-PBD in the TRAILS sample.

Results: The CBCL-MS had high internal consistency and satisfactory accuracy (area under the curve= 0.64) in this general population sample. Principal Component Analyses, followed by parallel analyses and confirmatory factor analyses, identified four factors corresponding to distractibility/disinhibition, psychosis, increased libido and disrupted sleep. This factor structure remained stable across all assessment ages. Logistic regression analyses showed that the CBCL-MS had significantly higher predictive ability than both the other scales.

Conclusions: Our data demonstrate that the CBCL-MS is a promising screening instrument for BD. The factor structure of the CBCL-MS showed remarkable temporal stability between late childhood and early adulthood suggesting that it maps on to meaningful developmental dimensions of liability to BD.

Introduction

Bipolar Disorder (BD) is a complex mental disorder affecting between 0.1% and 4.4% of the general population [1]. BD is the sixth leading cause of disability worldwide particularly amongst adolescents and young adults [2]. This is partly due to the typically early onset of BD with the majority of patients presenting between 19-25 years of age [1,3]. More important however is the failure in recognizing and treating BD particularly in the early stages of the disorder. The typical delay between onset and diagnosis is 5-10 years [4-6] and is associated with greater clinical severity, increased psychosocial morbidity and higher treatment costs [7-9]. Although mania is the diagnostic hallmark of BD [10, 11] the differential diagnosis from Major Depressive Disorder (MDD) is often difficult as BD is commonly dominated by depressive symptoms [12,13]. Furthermore, BD is also associated with high rates (between 60-80%) of psychotic symptoms during mood episodes [14,15]. High rates of psychotic symptoms have also been reported in young patients and confirm their role as a key symptom dimension of BD in adolescence [16, 17]. Additional diagnostic challenges arise from the symptomatic overlap between BD and Attention Deficit Hyperactivity Disorder (ADHD), which also presents with poor attentional and emotional regulation [18].

In response to the urgent need for the early identification of individuals at high risk for BD there have been several attempts to develop and validate screening instruments. In adults, one of the most widely studied screening instruments is the Mood Disorder Questionnaire (MDQ) [19], a self-report questionnaire based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for mania [10]. A positive MDQ screen is based on participants endorsing 7 or more lifetime manic symptoms, several co-occurring, resulting to moderate or serious functional impairment. In outpatient psychiatric settings the MDQ was reported to achieve sensitivity and specificity rates of 67%-83% and 86%, respectively [5]. Although specificity and sensitivity are theoretically independent of prevalence in practice as they are influenced by the clinical composition of the sample (e.g. proportion of severe to

mild cases) and interviewers' assumptions about the frequency of a disorder [20]; typically, in general population samples sensitivity is lower and specificity is higher than that reported in clinical populations. For example, the sensitivity and specificity of the MDQ in the general population are respectively 23-25% and 97-99% [21, 22]. Additionally, many individuals with MDD, anxiety disorders or ADHD screen positive on the MDQ [22, 23].

A significant number of screening instruments for juvenile BD have been developed and have been used mostly in clinical populations. These include the Parent version of the Young Mania Rating Scale (P-YMRS) [24], the Parent General Behavior Inventory (P-GBI) [25], the Adolescent General Behavior Inventory (A-GBI) [25], the Youth Self Report (YSR) [27], the Teacher Report Form (TRF) [28], the Child Mania Rating Scale (CMRS) [29], the Child Behaviour Checklist (CBCL) [30], and the Mood Disorder Questionnaire Adolescent Version (MDQ-A) [31]. The CBCL [30] is the instrument most commonly used to generate profiles relevant to BD in youth. The CBCL is a parent report checklist of 118 items mapping onto multiple aspects of psychopathology over a 6-month period [30, 32]. The CBCL items are grouped in eight behavioural domains: aggressive behaviour, anxiety/depression, attention problems, rule-breaking behavior, withdrawal/depression, somatic complaints, social problems and thought problems [30]. Different scales have been generated based on varied combinations of these behavioural domains. Of relevance to BD, are the Externalizing Scale (comprising items scores from the rule-breaking and aggressive behaviour domains) and the CBCL-Pediatric Bipolar Disorder scale (CBCL-PBD) (comprising scores from the aggressive behavior, anxiety/ depression and attention problems domains) [33]. The CBCL-PBD is also referred to as the Dysregulation Profile as it has been associated with disorder involving extensive behavioural and emotional dysregulation [34] including BD [35]. However all available instruments have limited specificity for BD as they have been associated with MDD, ADHD and anxiety disorders [36-40].

Therefore there is still a need for screening instruments for BD particularly for use in non-clinical populations of young individuals. In an attempt to address this need we developed and evaluated a new screening scale for BD in children and adolescents based on the CBCL 6-18 [30]. Despite the limited success of previous CBCL-based screening instruments for juvenile BD we decided to use it as the base of the new scale because of its cross-cultural generalizability [41]. However, instead of using summary scores of the existing behavioural domains we constructed this new scale following the methodology defined for DSM-oriented subscale development by Achenbach et al. (2003) [42]. Content validity of the new scale was evaluated by an expert panel of child and adolescent psychiatrists who selected 19 CBCL items that relate directly to the diagnostic criteria for mania as currently operationalized in the DSM-IV (details of the process are available in the supplemental material). The new scale called CBCL-Mania Scale (CBCL-MS) was tested for its psychometric properties, sensitivity and specificity on data from the TRacking Adolescents' Individual Lives Survey (TRAILS) [<http://www.trails.nl/en/>] [43]. TRAILS is a prospective study of an epidemiologically representative cohort of 2230 Dutch adolescents who were assessed with the full CBCL at age 11, 13 and 16. Clinical outcomes were evaluated at age 19 using the Composite International Diagnostic Interview (CIDI) [44]. We also compared the performance of the CBCL-MS against the CBCL-Externalising Scale and the CBCL-PBD to test whether it presents an improvement in terms of accuracy and predictive ability.

Methods

Participants

The sample consisted of participants of the TRacking Adolescents' Individual Lives Survey (TRAILS). The sampling procedure and cohort details for TRAILS have been previously described in detail [43] and can be found at the study website [<http://www.trails.nl/en/>]. Briefly, the cohort includes children born between 1 October 1989 and 30 September 1991 in a well-defined geographic area in the north Netherlands (information about the representativeness of the sample is included as supplemental material). Permission to use anonymised data from the TRAILS was granted by the study management committee and ethical approval was granted by the Dutch Central Committee on Research Involving Human Subjects (CCMO). All data were anonymised according to the TRAILS and the research office TNS NIPO [<http://www.tns-nipo.com/>] protocols.

Assessments

At ages 11, 13 and 16 years the parents or parent surrogates of TRAILS cohort members completed the CBCL 6-18. Each CBCL item was scored on a three point scale (0=not true, 1=somewhat or sometimes true, 2=very true or often true) on the basis of the preceding 6 months. At age 19 the diagnostic status of the TRAILS participants was ascertained using the Computer Assisted Personal Interview version 20 (CAPI) of the CIDI [<http://www.hcp.med.harvard.edu/wmhcdi/>]. The CIDI is a comprehensive, structured interview which was used by trained lay interviewers to assess mental disorders according to the definitions and criteria of the ICD-10 and the DSM-IV. It has high test-retest reliability for the diagnosis of BD type I (BD-I) [45] as well as excellent concordance rates with the Structured Clinical Interview for DSM-IV (SCID) for lifetime bipolar spectrum disorders [46]. Diagnostic assessments were conducted blind to participants' CBCL scores.

Child Behavior Check List - Mania Scale (CBCL-MS)

An expert panel of child and adult psychiatrists, based at the Institute of Psychiatry and the South London and Maudsley NHS Foundation Trust, independently screened all CBCL items to select those that correspond to the DSM-IV operational criteria for mania. As the diagnostic criteria for mania in DSM-IV and ICD-10 are identical [www.who.int/classifications/icd/en/GRNBOOK.pdf] this selection is applicable to both diagnostic systems. In addition, the panel considered CBCL items relating to psychotic-like experiences as childhood and adolescent psychotic-like experiences and high CBCL total scores are frequently associated with later development of mania [37-40]. Following consensus meetings, 19 items were selected for inclusion in the new CBCL-Mania Scale (CBCL-MS) (Table 1). Detailed information on the item selection procedure is included as supplemental material to this article. The scoring of the CBCL-MS at each assessment age was based on summing the scores of each of the 19 individual items. Scores were then standardized (T scores) following the scoring procedure recommended by Achenbach and Rescorla (2001) [32] using the TRAILS data as the standardization sample. Standardization of the CBCL scores for the CBCL-MS, as well as for other CBCL-based syndrome scales, was performed separately for each wave. The CBCL-MS and its scoring are available in Appendix 1.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics, Version 19 (www.spss.com) and MPlus 6.0 (www.statmodel.com).

Reliability and validity of the CBCL-MS

As the CBCL-MS is a new scale the consistency of its items at each assessment wave was evaluated using Cronbach's alpha. Cronbach's alpha is an index of the reliability of a scale and is calculated by means of the average correlation of the items of the scale. It takes values from 0 to 1 with higher scores indicating higher reliability [47]. In order to determine the number of factors that best describe the latent factor structure of the CBCL-MS at ages 11, 13 and 16 the following criteria were considered:

the shape of the scree plot, parallel analysis using a permuted data approach (number of data sets: 5000; confidence interval 95%) [48, 49], the Kaiser criterion as an upper bound for the number of factors to be retained, and the interpretability of the obtained factor structure. In order to conduct the parallel analysis, principal components analysis (PCA) was performed first, with oblique or varimax rotation (as appropriate). PCA is a dimensionality reduction technique which reduces the number of items (observed variables) to a number of principal components which account for most of the variance of the observed variables. We selected PCA instead of an Exploratory Factor Analysis (EFA) as it represents a less conservative data reduction technique [50]. The main difference between the two is that EFA assumes error variance by estimating the commonalities, while in a PCA framework they are assumed to be initially 1. Yet, the relationship between the observed variables and the underlying constructs was then confirmed using a Confirmatory Factor Analysis (CFA) which is traditionally used to test the relationship pattern statistically. For each assessment age, the model fit of the final solutions was assessed using two fit indices, the Root Mean Square Error of Approximation (RMSEA) (cut-off values less than 0.06 indicate good fit and values as high as 0.08 represent reasonable errors of approximation in the population) and the Confirmatory Fit index (CFI) (cut-off values above 0.90-0.95 indicate good fit) [51].

Sensitivity and Specificity of the CBCL-MS

Omnibus tests using the standardized T scores of the CBCL-MS, the CBCL-Externalizing Scale and the CBCL-PBD and were performed to compare the scores of participants with CIDI diagnoses of BD type I (BD-I) to those of healthy participants and participants with other CIDI diagnoses that are considered relevant to BD as they involve mood abnormalities (anxiety or depression), or inattention and behavioral disruption. We present data on Major Depressive Disorder (MDD), General Anxiety Disorder (GAD), and ADHD as the most pertinent exemplars. Finally, Receiver Operating Characteristics (ROC) curves [52] were used to calculate the diagnostic efficiency of the CBCL-MS, CBCL-

PBD and CBCL-Externalizing Scale. A ROC curve illustrates the sensitivity (true positive rate) of different cut-offs on the y axis and the 1-specificity (false positive rate) of the corresponding cut-offs on the x axis. In the ROC analysis, the area under the curve (AUC) statistic provides a summary of test performance. AUC values range from 0 to 1 with higher values denoting greater discriminative power and diagnostic efficiency. The focus of the analysis was on BD-I as the usefulness of a test with poor discriminative ability for core syndromal BD would be questionable. However, we also performed ROC analysis using a more expanded definition of caseness that also included BD type II (BD-II) and hypomania with no major depressive episode.

Results

TRAILS participants with BD

At age 19, 56 of the TRAILS participants were diagnosed with BD-I. Sixteen of the BD-I cases had a previous diagnosis of BD-II while 34 had attracted other psychiatric diagnoses prior to being diagnosed with BD; seventeen had a single previous diagnosis either for Oppositional Defiant Disorder (ODD) (n=5) or Conduct Disorder (CD) (n=5) or ADHD (n=4) or GAD (n=3). Of the remaining seventeen BD cases, eleven had two prior diagnoses (ADHD/ODD=2, ADHD/CD=1, ADHD/GAD=1, ADHD/MDD=1, ODD/CD=3, ODD/GAD=2, ODD/MDD=1), five had three prior diagnoses (ODD/CD/GAD=3, ODD/CD/ADHD=2) and one had four (ODD/CD/ADHD/GAD).

Internal consistency and factor structure of the CBCL-MS

Reliability analysis demonstrated high internal consistency for the 19 items of the CBCL-MS at all assessment ages (Cronbach's $\alpha \geq 0.80$; total item correlation > 0.37). A PCA of the CBCL-MS data assessed at age 16 extracted four factors corresponding to: (1) distractibility/ disinhibition (2) psychotic symptoms (3) increased libido (4) disrupted sleep (Figure 1). These factors were plausible and interpretable as items' loading segregated among the four factors as shown in Table S1, available on line. The factor structure represents the orthogonal solution of the PCA, as the factors extracted using oblique rotation were only weakly correlated ($r < 0.3$). The Parallel analysis and Kaiser's criterion both supported the retention of four factors. The scree plot of the extracted eigenvalues from the parallel analysis is given in supplemental Figure S1, available on line. Analyses of the CBCL-MS data at ages 11 and 13 years resulted in an almost identical factor structure indicating longitudinal stability of this solution (Tables S1, S2 and S3, supplemental material available on line). Confirmatory factor analyses further supported the goodness of fit of 4-factor structure (RMSEA ≤ 0.05 and CFI ≥ 0.92).

Discriminative ability and performance of the CBCL-MS

Table 2 presents the mean total and CBCL-MS factor scores for TRAILS participants who were diagnosed with BD-I and for those who did not have any lifetime psychiatric diagnosis. Participants with BD had significantly higher mean total CBCL-MS scores compared with participants with MDD ($n=178$; $p=0.002$) and GAD ($N=20$; $p=0.004$) but not ADHD ($N=26$; $p>0.05$) (Figure 3).

The ROC curve analysis on the CBCL-MS data at age 16 is illustrated in Figure 2. The AUC was 0.64 ($p<0.01$) which represents a satisfactory performance for a general population sample with low prior probability of true positives. The AUC remained unchanged when caseness was expanded to include BD-II and hypomania without major depressive episode. Moreover, the total CBCL-MS score performed better than the scores of each individual factors used independently or sequentially (details in supplemental material, Table S4 and S5).

We identified two cut-off scores that respectively optimise sensitivity or specificity that could be selected depending on the intended use. For a CBCL-MS cut-off score of 43 (i.e. one standard deviation below the population mean) sensitivity and specificity were 82% and 30% respectively. For a CBCL-MS cut-off score of 60 (i.e. one standard deviation above the population mean) sensitivity and specificity were 33% and 90% respectively. A CBCL-MS cut-off score of 70 corresponds to the clinical cut-off score for CBCL subscales (i.e. 2 standard deviations above the populations mean) proposed by Achenbach et al. (2001) [32] and yields sensitivity and specificity values of 23% and 97% respectively.

Comparison to CBCL-PBD: TRAILS participants with BD-I had significantly higher CBCL-PBD mean scores (56.51, $SD=15.91$) in comparison to healthy participants (49.79, $SD=9.69$) but not compared to participants with MDD ($p=0.54$), GAD ($p=0.51$) or ADHD ($p=0.37$). ROC curve analysis showed a moderate ability of the CBCL-PBD in distinguishing BD-I cases from healthy TRAILS participants ($AUC=61\%$, $p=.002$).

Comparison to the Externalizing scale of the CBCL: Externalizing scale mean scores were significantly higher for TRAILS participants with BD-I (58.49, SD=18.27) in comparison to healthy participants (48.44, SD=8.25) and participants with MDD (52.00, SD=9.80) or GAD (50.52, SD=7.80), but not compared to participants with ADHD ($p=.23$). ROC analysis showed that the Externalizing scale had AUC=63%, $p=.003$ when discriminating between TRAILS cases with BD-I and healthy participants.

A forward stepwise logistic regression model showed that the CBCL-MS had significantly increased ability to predict BD-I compared to the CBCL-PBD (Wald $\chi^2= 12.69$, $p<.001$) and the CBCL-Externalizing Scale (Wald $\chi^2= 3.47$, $p=.05$).

Discussion

We present data on the psychometric properties and discriminative ability of the CBCL-MS, a new DSM based screening scale for BD-I based on the CBCL. We demonstrate that the new scale has excellent psychometric properties; its discriminative ability and accuracy in a general population sample of young people represent an improvement over other commonly used scales particularly CBCL-PBD and the CBCL-Externalizing Scale.

Prevalence and Characteristics of TRAILS participants with BD

The lifetime prevalence of BD-I in the TRAILS sample was 2.5% which is identical to that reported in a recent epidemiological study of US adolescents [53]. Also consistent with previous literature, nearly 61% of BD-I cases in the TRAILS sample had prior diagnoses associated with disruptive behaviour most commonly ADHD and ODD [18, 53-56].

Reliability and validity of the CBCL-MS

The reliability of the CBCL-MS as assessed using Cronbach's alpha was satisfactory (>80%) at all assessment points. The main disadvantage of using Cronbach's alpha arises from the fact that it is based on the inter-item correlations and can therefore be affected by the homogeneity of subject responses on the items. Yet, it is considered to be the most widely used index of reliability due to its power, simplicity and ease of interpretation [57].

Moreover, the CBCL-MS satisfied different validity criteria necessary in the development of new scales. Firstly, the items of the CBCL-MS were selected by an expert panel to map onto DSM-IV diagnostic criteria for Mania, thus ensuring face and content validity. In addition, construct and criterion validity of the CBCL-MS was established by means of PCA, ROC analysis, regression models and ANOVAs. Construct validity refers to the degree to which explanatory concepts of the scale account for the

performance of the test and how plausible they are while criterion validity refers to how well a set of variables predicts an outcome [58]. The extraction of four plausible and interpretable factors corresponding to symptoms dimensions of BD as described in previous research [56, 59-62], the high discriminative ability of the CBCL-MS to distinguish between BD cases and healthy controls as well as a significant regression model between the CBCL-MS and BD-caseness provided support for the construct and criterion validity of the CBCL-MS. Moreover, external validity has been defined in the seminal work of Campbell and Stanley (1963) as an index of the generalizability of the findings to other samples, times, measures and settings [63]. The external validity of the CBCL-MS was therefore established for the CBCL-MS by the representativeness of the sample (Table S6) and the extraction of the same principal component structure across assessment points. The association between the scores of the CBCL-MS and other instruments measuring manic symptomatology was not assessed in this study as the CBCL was the only available instrument; therefore, the convergent and divergent validity of the CBCL-MS is yet to be established in future studies.

Factor Structure of the CBCL-MS reveals developmentally meaningful dimensions of liability to BD

The structural model of the CBCL-MS consisted of four factors. These factors correspond to dimensions of distractibility/disinhibition, psychosis, increased libido and disrupted sleep. The factor structure of the CBCL-MS showed remarkable temporal stability between the ages of 11 to 16 which strongly supports the notion that it defines developmentally meaningful dimensions of liability to BD. This report is the first to describe developmental dimensions of liability to BD. All other studies have focused on symptom dimensions during acute manic episodes in patients with established BD [56-59-62]. Nevertheless, there are significant similarities. Cassidy and colleagues identified 5 factors in acute mania of which the “psychomotor pressure”, “psychosis” and “increased hedonic” factors correspond to the distractibility/disinhibition, psychosis and increased libido factors in this study [59]. Picardi et al [60] defined a four factor

structure of acute mania based on the Brief Psychiatric Rating Scale. The factors they named “mania” and “disorganisation” include items similar to the distractibility/disinhibition factor identified here. In addition their “positive symptoms” factor overlaps with the psychosis factor in this study. Cassano et al [61] identified 5 factors in acute mania of which “psychomotor agitation” and “psychoticism” correspond to the factors of distractibility/disinhibition and psychosis in the TRAILS cohort. All three studies also defined factors relating to dysphoric/euphoric mood and aggression that seem to be present only during acute mania and may not represent an independent dimension of developmental liability to BD.

In this study we treated each measurement wave separately under the assumption of measurement invariance. Measurement invariance represents the extent to which the psychometric properties of the observed variables can be generalised across groups or over time. Commonly, measurement invariance is assumed to hold in any statistical analysis but it can also be tested explicitly under latent modelling frameworks, e.g. EFA. Milfont et al. (2010) have described different types of invariance for multigroup analyses which can also be expanded to assess longitudinal invariance [64]. There are two main types of longitudinal invariance; a) measurement invariance including invariance of factor loadings, item intercepts and residual variances across assessments; and b) structural invariance including invariance of the factor variances, covariances and means over time. The first type of measurement invariance examines whether the construct is measured in the same way at each assessment point while structural invariance assesses differences in the distribution and the means of the constructs over time. These types of analyses exceeded the scope of this study as the PCAs and parallel analyses provided support for the structure of the components of the CBCL-MS extracted across assessment points and they were comparable to the aforementioned research [56, 59-62]. Nonetheless, future studies on the longitudinal stability of BD dimensions should address issues of measurement invariance within EFA frameworks.

Discriminative ability of the CBCL-MS

The overall accuracy was 0.64 for the CBCL-MS and CBCL-Externalising Scale and 0.61 for the CBCL-PBD. The results of the logistic regression comparing the three scales showed that the CBCL-MS was statistically better in predicting BD outcome.

As seen by the ROC, different cut-off scores will influence the sensitivity and specificity of the CBCL-MS. A cut-off score of 43 increases sensitivity while maintaining acceptable specificity while increasing the cut-off score to 70 increases specificity while maintaining acceptable sensitivity. In general population screening the emphasis is usually on specificity thus selecting individuals at highest risk for detailed follow-up assessments. To illustrate this point, in a hypothetical community sample of 10000 youth with a 2.5% prevalence of BD we would expect 250 individuals to have BD (true positives). A CBCL-MS score of 70 or above will correctly identify 8,775 individuals (90% of this sample) as not having BD (true negatives). At the same threshold, 1,050 individuals will be classified as possible cases. This sample will include 75 true cases of BD (true positives) and 975 individuals without BD (false positives). At first glance, one might be concerned about the number of false positive cases. However, those scoring above 70 in the CBCL-MS were at a six-fold increased risk for BD (Positive Predictive Value: 16.57%; Negative Predictive Value: 98.01%) compared to the rest of the sample and therefore they represent a high risk group. The field of early intervention in BD is currently in its infancy [65] but as effective therapies become available [66] scales such as the CBCL-MS may contribute to the identification of those at high risk.

None of the scales differentiated participants with BD from those with ADHD in terms of mean scores. The relationship between these two disorders is complex. Available evidence suggests at least partially overlapping aetiology and pathophysiology for BD and ADHD because of familial co-segregation of the two disorders [67, 68], commonalities in their neurobiological correlates [18, 69, 70], and frequent comorbidity [18]. Additionally, there is significant overlap in the symptoms of the two disorders particularly with regards to increased activity, talkativeness and mood dysregulation

[10, 11]. Two main features distinguishing BD from ADHD have been proposed. Geller and colleagues emphasized the importance of either elevated mood or grandiosity for a diagnosis of mania [71]. However, in our study these symptoms clustered with others in one factor and did not differ across the two diagnostic categories. Others have suggested that episodicity is more indicative of BD than ADHD [72] but this distinction seems less clear in children and adolescents [53]. It is therefore possible that scales based on observed behaviour lack assay sensitivity in distinguishing between BD and ADHD.

Methodological Issues and Future Directions

The present study has a number of strengths and limitations. The TRAILS sample is representative of the population of young people in the Netherlands (supplemental Table S6). The prevalence of BD in the TRAILS is nearly identical to that of general population samples elsewhere [1,53] which supports the generalizability of findings. Case ascertainment in the TRAILS does not depend on help-seeking behaviour or concern about impairment or severity and thus the sample is free from referral bias present in clinical populations. However, the CIDI although widely used is designed for lay interviewers who rely on its structured format and may not probe or interpret participant responses further. Case ascertainment was conducted at age 19. Since participants have not yet passed the entire period of risk for BD it is possible that further cases of BD may present in the future.

The CBCL-MS performed well within the context of a general population sample, it represents an improvement on available scales and could contribute to future public health initiatives for the identification of youth at high risk for BD. Its accuracy is moderate and in the same broad range of the other CBCL-based screening instruments. Although it could be argued that this reflects limitations in the CBCL we would suggest that behavioural ratings alone are unlikely to provide us with high levels of accuracy in case identification for BD or any mental disorder.

However a great strength of this study was the availability of CBCL assessments at multiple time points from late childhood to early adulthood. This allowed us to test the temporal stability of the CBCL-MS factors which supports the validity of these dimensions as developmentally meaningful premorbid indicators of BD.

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Figure 1. Factors and Factor Loadings of the Child Behavior Checklist-Mania Scale

Figure 2. Receiver Operating Characteristics curve of the Child Behavior Checklist-Mania Scale for Bipolar Disorder vs. healthy TRAILS participants

Figure 3. Child Behavior Checklist-Mania Scale Scores in TRAILS Participants

Table 1. Child Behavior Checklist-Mania Scale items and corresponding core and extended DSM-IV criteria for Mania

CBCCL Items	DSM-IV criteria for Mania
Core Symptoms	
37. Gets in many fights	A distinct period of abnormally and persistently elevated, expansive or irritable mood
87. Sudden changes in mood or feelings	
96. Thinks about sex too much	Inflated self-esteem or grandiosity
74. Showing off or clowning	
94. Teases a lot	Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
76. Sleeps less than most kids	
100. Trouble sleeping	More talkative than usual or pressure to keep talking
93. Talks too much	
104. Unusually loud	Flight of ideas or subjective experience that thoughts are racing
78. Inattentive or easily distracted	
10. Can't sit still, restless or hyperactive	Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
60. Plays with own sex parts too much	
41. Impulsive or acts without thinking	Increase in goal-directed activity (at work, at school, or sexually) or psychomotor agitation
59. Plays with own sex parts in public	
Extended Symptoms	
34. Feels others are out to get him/her	Delusions
85. Strange ideas	
89. Suspicious	Hallucinations
40. Hears sound or voices that aren't there	
70. Sees things that aren't there	

Table 2. Child Behavior Checklist-Mania Scale total and Factor Scores in TRAILS participants with Bipolar Disorder (BD) and healthy participants

	BD participants (N=56)	Healthy Participants (N=1201)	
	Mean Score (Standard Deviation)		p
Total CBCL-MS	57.28 (16.08)	49.33 (8.95)	<0.001
Distractibility/Disinhibition	56.01 (14.71)	49.18 (8.98)	<0.001
Psychotic Symptoms	56.19 (20.20)	49.44 (8.84)	<0.001
Increased Libido	51.99 (12.28)	49.48 (8.88)	0.088
Disrupted Sleep	54.42 (12.28)	49.63 (9.33)	0.002

Figure 1. Factors and Factor Loadings of the Child Behavior Checklist-Mania Scale

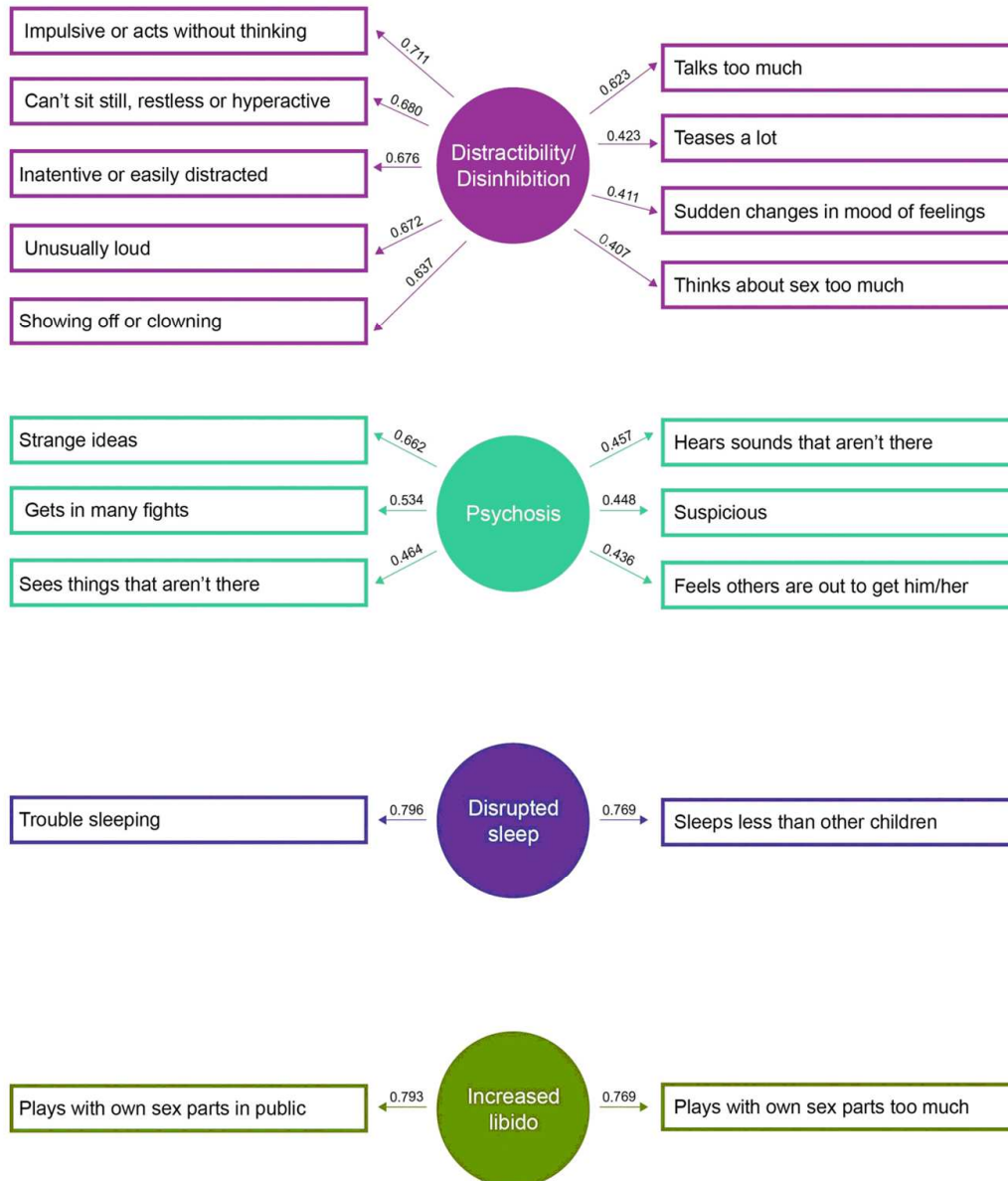


Figure 2. Receiver Operating Characteristics curve of the Child Behavior Checklist-Mania Scale for Bipolar Disorder vs. healthy TRAILS participants

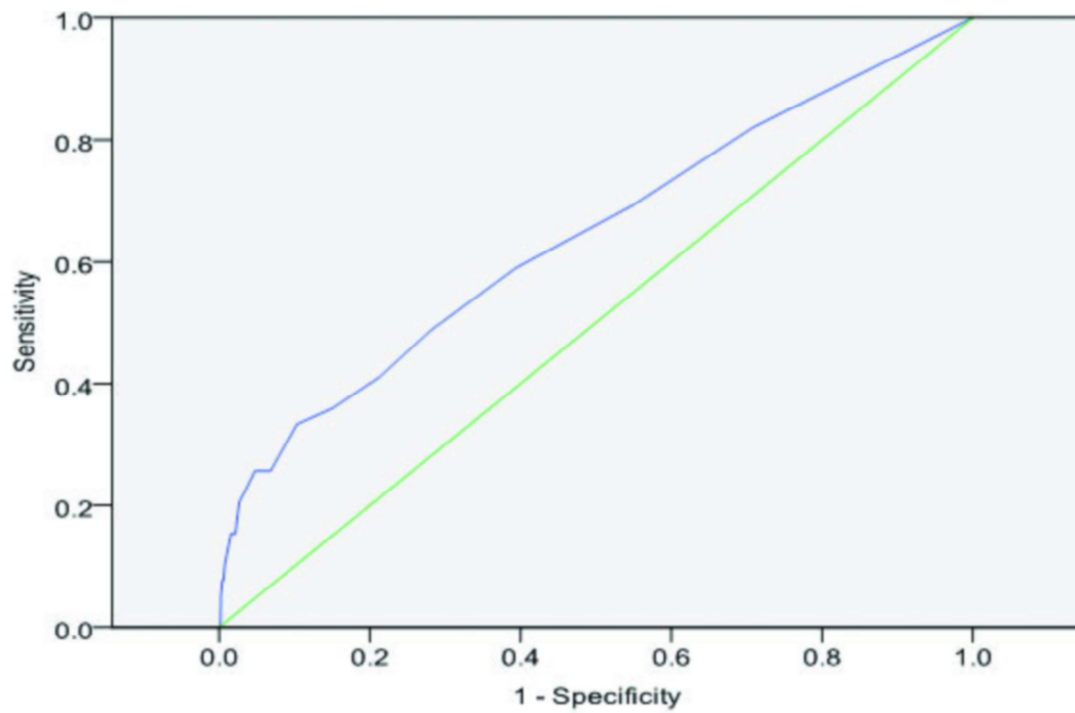
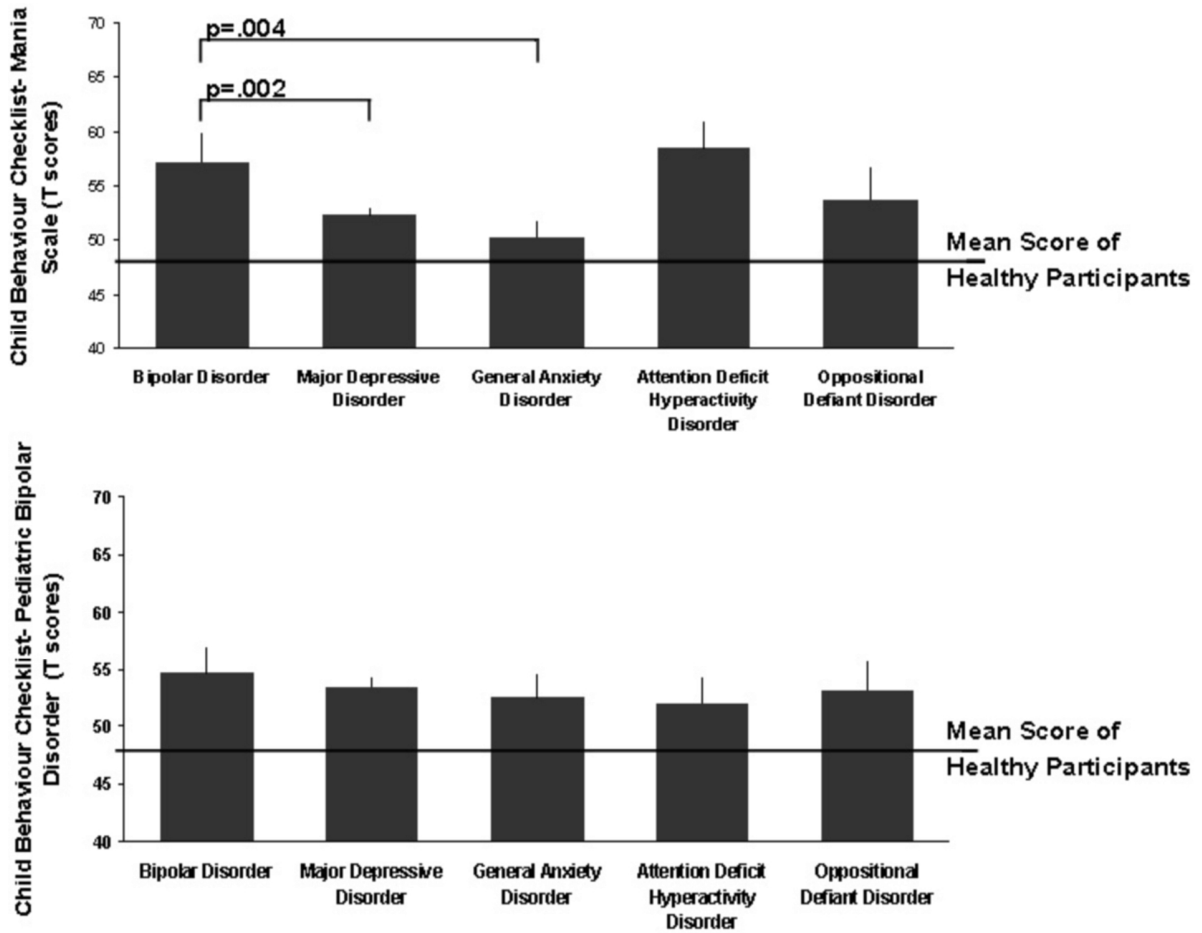


Figure 3. Child Behavior Checklist-Mania Scale Scores in TRAILS Participants



Supplemental Material

Selection of Items

We followed a typical content validity procedure (Grant & Davis, 1997; Lengua et al, 2001) which involves content experts who judge each item of an instrument against the definition of the domains intended to measure and score its relevance on a 4-point scale ranging from 1 (irrelevant) to 4 (highly relevant). In our study, content validity was assessed by a panel of 10 qualified child and adolescent psychiatrists (average number of years of clinical and research experience: 8; range: 4—20 years). These experts were representative of the professional settings (inpatient, outpatient, academic) within the South London and Maudsley NHS Foundation Trust. They rated the relevance of each item from the total item pool of the CBCL 6-18 on a scale of 1-4 against each of the symptom domains of mania as defined in the DSM-IV. The content validity index (CVI) for each item was established by calculating the proportion of experts scored it as relevant (score 3) or highly relevant (score 4) for any of the domains. A minimum item CVI of 0.80 (Grant & Davis, 1997) was required for inclusion in the second stage where final item inclusion to the CBCL-MS was based on unanimous agreement.

Psychometric properties of CBCL-MS across ages

Reliability analyses demonstrated high internal consistency for the 19 items of the CBCL-MS at all assessment ages (Cronbach's $\alpha \geq 0.80$; item total correlation > 0.37). PCA analyses of the CBCL-MS data at ages 11, 13 and 16 years resulted in an almost identical factor structure and explained 48.18%, 46.06% and 44.94% of the variance of the items respectively. The four factors corresponded to: (1) distractibility/ disinhibition (2) psychotic symptoms (3) increased libido (4) disrupted sleep. Items' loading for the four factors are shown in Table S1-S3. Parallel analyses and Kaiser's criterion both supported the retention of four factors. The scree plot of the extracted eigenvalues from the parallel analysis at age 16 is given in Supplemental Figure S1. Fit indices of Confirmatory Factor Analyses (CFA) established good fit of the data [Root Mean Square Error of

Approximation (RMSEA) values were 0.04, 0.04 and 0.05, and Confirmatory Fit index (CFI) values were 0.97, 0.96 and 0.92 for the three assessment points respectively].

Figure S1. Scree Plot of parallel analysis at age 16

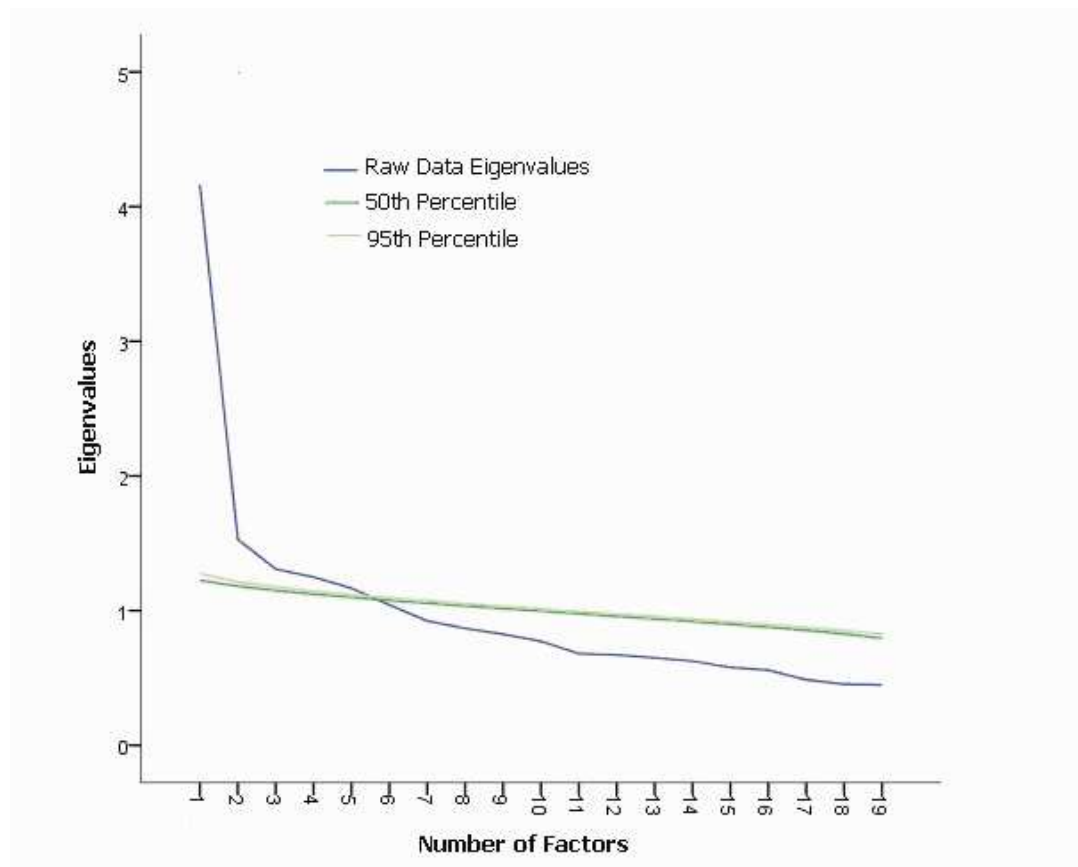


Table S1. Items, factors and item loadings of the CBCL-MS at age 16

Manic Items	Distractibility/ Disinhibition	Psychotic Symptoms	Disrupted Sleep	Increased Libido
41. Impulsive or acts without thinking	.711	.109	.043	.025
10. Can't sit still, restless or hyperactive	.680	.053	.081	.108
78. Inattentive or easily distracted	.676	.002	.117	.047
104. Unusually loud	.672	.177	.038	.073
74. Showing off or clowning	.637	.092	.018	.070
93. Talks too much	.623	.007	.103	-.047
94. Teases a lot	.423	.390	-.145	.159
87. Sudden changes in mood or feelings	.411	.299	.237	-.093
96. Thinks about sex too much	.407	-.026	.201	.001
85. Strange ideas	.028	.662	.301	-.101
37. Gets in many fights	.290	.534	-.131	.225
70. Sees things that aren't there	-.027	.464	.326	-.054
40. Hears sound or voices that aren't there	-.074	.457	-.054	.137
89. Suspicious	.406	.448	.150	-.169
34. Feels others are out to get him/her	.384	.436	.055	-.108
100. Trouble sleeping	.162	.127	.796	.030
76. Sleep/s less than most kids	.209	.038	.769	.097
59. Plays with own sex parts in public	.029	.109	.055	.793
60. Plays with own sex parts too much	.086	-.043	.038	.749

Table S2. Items, factors and item loadings of the CBCL-MS at age 13

Manic Items	Distractibility/ Disinhibition	Psychotic Symptoms	Increased Libido	Disrupted Sleep
41. Impulsive or acts without thinking	.704	.055	.014	.061
104. Unusually loud	.696	-.022	.024	.108
10. Can't sit still, restless or hyperactive	.695	-.041	.060	.052
78. Inattentive or easily distracted	.680	.068	.050	.080
74. Showing off or clowning	.671	.126	-.021	-.029
93. Talks too much	.597	-.033	-.035	.158
94. Teases a lot	.561	.213	.120	-.053
87. Sudden changes in mood or feelings	.489	.169	-.013	.226
89. Suspicious	.406	.394	-.087	.152
37. Gets in many fights	.399	.273	.119	-.122
96. Thinks about sex too much	.313	.176	.272	-.048
70. Sees things that aren't there	-.003	.789	-.063	.025
40. Hears sound or voices that aren't there	-.036	.664	.140	.056
34. Feels others are out to get him/her	.116	.497	.050	.095
85. Strange ideas	.347	.371	-.023	.107
60. Plays with own sex parts too much	-.017	.076	.842	.045
59. Plays with own sex parts in public	.054	-.029	.825	.015
76. Sleeps less than most kids	.097	.117	.014	.827
100. Trouble sleeping	.125	.115	.031	.803

Table S3. Items, factors and item loadings of the CBCL-MS at age 11

Manic Items	Distractibility/ Disinhibition	Psychotic Symptoms	Disrupted Sleep	Increased Libido
104. Unusually loud	.750	.128	.049	.055
74. Showing off or clowning	.706	.140	.046	.048
10. Can't sit still, restless or hyperactive	.681	.017	.077	.055
78. Inattentive or easily distracted	.678	.076	.064	.049
41. Impulsive or acts without thinking	.676	.138	.034	.098
94. Teases a lot	.628	.078	.041	.031
93. Talks too much	.585	.047	.072	.075
87. Sudden changes in mood or feelings	.532	.306	.094	-.086
37. Gets in many fights	.524	.037	.001	.179
70. Sees things that aren't there	.027	.706	.073	.053
40. Hears sound or voices that aren't there	-.071	.685	.018	.182
85. Strange ideas	.185	.539	.070	.086
89. Suspicious	.329	.483	.100	-.039
34. Feels others are out to get him/her	.392	.470	.031	-.108
76. Sleeps less than most kids	.138	.067	.857	.030
100. Trouble sleeping	.065	.166	.843	.009
60. Plays with own sex parts too much	.082	.041	-.034	.825
59. Plays with own sex parts in public	.003	.214	-.050	.703
96. Thinks about sex too much	.267	-.050	.174	.476

Discriminative ability of the CBCL-MS

We examined the discriminative ability of each factor and of the total CBCL-MS score at the cut-off point of 1 standard deviation above their corresponding population mean. The results are shown in Table S4.

Table S4. Discriminative ability of the total CBCL-MS and its factors

	Area Under the curve (p value)	Sensitivity	Specificity
CBCL-MS	0.64 (0.003)	0.33	0.90
Distractibility/Disinhibition	0.63 (0.004)	0.25	0.87
Psychosis	0.57 (0.097)	0.17	0.94
Increased Libido	0.53 (0.403)	0.17	0.98
Disrupted Sleep	0.56 (0.167)	0.23	0.90

The total CBCL-MS score had better discriminative ability than each of the individual factor scores. We then tested whether sequential application of the factors improved predictive ability for BD over that achieved using the composite CBCL-MS alone. We conducted two regression analyses, a stepwise forward logistic regression model using the 4 factors as predictors and a regression model using the total CBCL-MS score as the single predictor. The final model of the stepwise forward logistic regression contained only the distractibility/disinhibition factor suggesting that none of the remaining three factors improved predictive accuracy (all p values of the competing regression models > .05). However, the Nagelkerke R² for this model was 1.2% less than that obtained from a regression model using the total CBCL-MS score as a single predictor variable. Results of the two regression models are summarized in Table S5 below.

Table S5. Regression Models

	Predictor Variables	B	OR	95%CI	p	χ^2
Model 1^a	Distractibility/Disinhibition	.05	1.05	1.03-1.08	<.001	15.19, p<.001
	Psychotic Symptoms	--	--	--	.07	
	Disrupted Sleep	--	--	--	.14	
	Increased Libido	--	--	--	.74	
Model 2	CBCL-MS	.06	1.06	1.03-1.08	<.001	18.92, p<.001

^aStepwise Forward Regression Model

Therefore, the CBCL-MS appears to be better in terms of its predictive accuracy for BD as a single composite scale in comparison to its factors either used individually or in tandem.

Representativeness of the TRAILS sample

The TRAILS cohort was identified through birth and school registers in the 5 northern municipalities of Holland. Recruitment was based on entire schools participating; 91% of all the schools in the municipalities agreed to take part. Table S6 shows that key variables regarding representativeness of the TRAILS cohort are comparable to those from the 2001 Dutch national census.

Table S6. Characteristics of TRAILS participants at enrolment compared to the 2001 national census data available online from the Centraal Bureau voor de Statistiek (www.cbs.nl)

	TRAILS	2001 Dutch Census
% Girls	50.8%	48.8% ¹
% White European	89.4%	93.2% ¹
Lower parental education ²	32.6%	30.6%
% children living with both parents ³	84.5%	84%
Median disposable household income	21780 Euros	20700 Euros

¹The census reported on the 10-15 years age range; ²Defined as having completed up to lower half of secondary school ³ includes married and cohabiting couples

Data Availability

The collection, management and distribution of the TRAILS data are coordinated by the University Medical Center Groningen, The Netherlands. Details can be found at the study website: www.trails.nl. The study management committee is open to requests by all researchers for the use of anonymised data from the TRAILS. Further information about the process can be requested via e-mail: trails@med.umcg.nl.

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Appendix

Child Behaviour Checklist – Mania Scale (CBCL-MS)

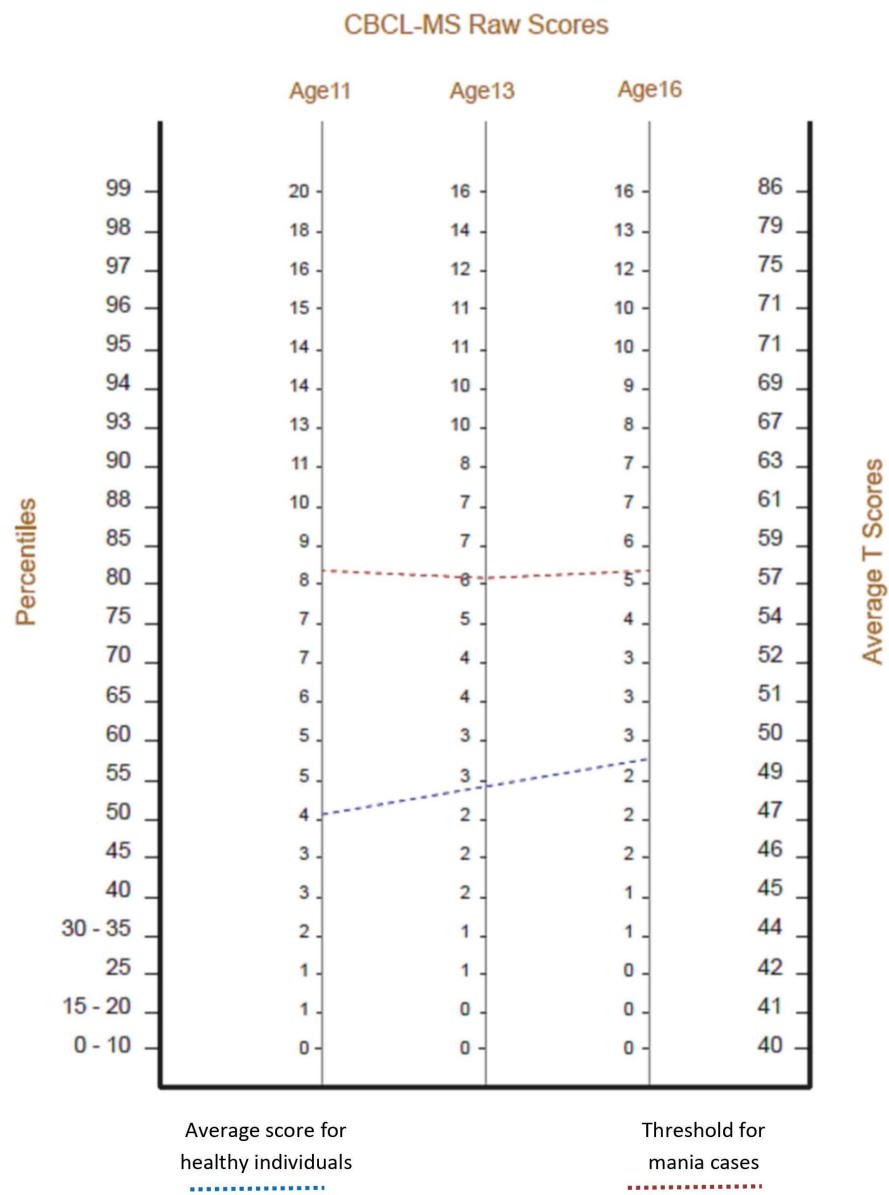
Below is a list of items that describe children and youths. For each item that describes your child **now or within the past 6 months**, please circle the **2** if the item is **very true or often true** of your child. Circle **1** if the item is **somewhat or sometimes true** of your child. Circle **0** if the item is **not true** of your child. Please answer all items as well as you can, even if some do not seem to apply to your child.

0=not true 1=somewhat or sometimes true 2= very true or often true

0	1	2	Can't sit still, restless or hyperactive
0	1	2	Feels others are out to get him/her
0	1	2	Gets in many fights
0	1	2	Hears sound or voices that aren't there
0	1	2	Impulsive or acts without thinking
0	1	2	Plays with own sex parts in public
0	1	2	Plays with own sex parts too much
0	1	2	Sees things that aren't there
0	1	2	Showing off or clowning
0	1	2	Sleeps less than most kids
0	1	2	Inattentive or easily distracted
0	1	2	Strange ideas
0	1	2	Sudden changes in mood or feelings
0	1	2	Suspicious
0	1	2	Talks too much
0	1	2	Teases a lot
0	1	2	Thinks about sex too much
0	1	2	Trouble sleeping
0	1	2	Unusually loud

Items listed correspond in ascending order to items 10, 34, 37, 40, 41, 59, 60, 70, 74, 76, 78, 85, 87, 89, 93, 94, 96, 100, 104 of the CBCL (6-18) by Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. Research Center for Children, Youth and Families. University of Vermont, Burlington, VT: 2001.

CBCL-MS Scoring Sheet



5 Alarm Symptoms in the early diagnosis of bipolar disorder: a population based cohort study

Submitted to the *American Journal of Psychiatry*

Alarm symptoms in the early diagnosis of bipolar disorder: a population based cohort study

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Abstract

Objective: Screening and clinical guidance development for medical disorders are based on “alarm symptoms”, clinical features known to predict disease. Our aim was to define and evaluate the concept of “alarm symptoms” for broadly defined Bipolar Disorder (BD) in a population based study.

Methods: We used latent class analysis to model the relationship between subclinical manic symptoms collected with the Child Behaviour Checklist-Mania Scale (CBCL-MS) at age 11 years and syndromal diagnosis of BD by age 19 years in a cohort of 2230 Dutch adolescents participating in the TRacking Adolescents’ Individual Lives Survey. Sex, socioeconomic status, cognitive ability, parental psychiatric morbidity and family dysfunction were also considered in the model.

Results: LCA of CBCL-MS items identified three classes, representing an asymptomatic class (n=862), a mildly symptomatic class (n=845) and a highly symptomatic class (n=199). The odds ratio of subsequent BD was 2.66 (95% CI 1.41-5.02) in the mildly and 7.1 (95% CI 3.31-15.11) in highly symptomatic class. The risk for depression, anxiety and substance abuse disorders was not associated with class membership. Significant deviance in mood lability, impulsivity, inattention and increased activity and speech were identified as “alarm symptoms”; this symptom cluster had a positive and negative predictive value for BD of 13.2% and 96.3% respectively.

Conclusions: Our results support the concept of “alarm symptoms” in BD, as highly deviant childhood manic symptoms were associated with a subsequently greatly elevated risk of BD, and for initiatives to identify underlying BD at an earlier and more amenable stage.

Introduction

There is currently much interest in the childhood antecedents of Bipolar Disorder (BD) based on three lines of evidence. The first line derives from follow-back studies of adult patients with BD; the majority report subthreshold symptoms in childhood and adolescence and date the onset of their illness between the ages of 13-18 years (1-3). The second line is based on prospective evaluations of individuals at high risk for BD by virtue of having at least one affected parent (4). Offspring of BD parents often present with mood lability, depression, elevation or irritability, changes in energy levels and decreased sleep (5-7). Cognitive problems and family dysfunction further increase the risk of subsequent BD (8, 9). The third line of evidence comes from studies that examined the prevalence and predictive value of subclinical manic symptoms in general population samples of youth using repeated assessments over follow-up periods of 10-16 years (10-14). Subclinical manic symptoms were found to be relatively common (5-25%) (11, 12) and were mostly transient (13, 14). Their predictive value for BD was limited except when symptoms persisted throughout adolescence (13). However, the future course of subclinical manic symptoms is unknowable and thus of limited value in the clinical evaluation of individuals presenting in childhood. In addition, subclinical childhood manic symptoms showed modest associations with childhood diagnoses of disruptive behavior disorders and adult diagnoses of anxiety, depression and substance abuse (11).

Subclinical manic symptoms in childhood are therefore imperfect predictors of clinical outcome. The problem of imperfect prognostic indicators is not unique to psychiatry but applies to multiple fields of medicine. The early detection of cancer is a key example. Most of the early symptoms of cancer are non-specific (e.g. weight loss, fatigue, persistent coughing) and highly prevalent in the general population (15). Nevertheless, clinical features considered predictive of malignancy, often termed “alarm symptoms”, form the basis of public awareness campaigns and of clinical guidelines (www.cancer.org). Conventionally, “alarm symptoms” with a positive predictive value (i.e. the probability that an individual with alarm symptoms has a malignant disease) of

≥5% are used to identify those in need of further evaluation (16). There is no similar provision for BD despite increased mortality rates and reduced life expectancy by 12-14 years (17). Extending the concept of “alarm symptoms” to BD may provide a useful framework for the evaluation of subclinical manic states in youth in order to identify underlying BD at an earlier and more amenable stage.

To address this issue, we examined data from the TRacking Adolescents’ Individual Lives Survey (TRAILS) (www.trails.nl) which followed a representative general population cohort of 2230 Dutch children from age 11 to age 19 years (18, 19). Our objectives were to (a) specify the number of underlying categories (latent classes) of TRAILS participants according to their subclinical manic symptoms profile, (b) ascertain the predictive value of class membership for subsequent syndromal BD, (c) to define “alarm symptoms” for BD based on the predictive value of the subclinical manic symptom profile of each class and, (d) to determine the contribution to class membership of key risk factors concerning cognitive ability, parental psychiatric morbidity and family dysfunction.

Methods

TRAILS Cohort

The TRacking Adolescents' Individual Lives Survey (TRAILS) (www.trails.nl) is a prospective longitudinal study of a representative population cohort of 2230 individuals born in northern Netherlands between 1 October 1989 and 30 September 1991. Details of the TRAILS design, sampling and assessments have been described elsewhere (18) and are summarised in supplemental material and supplemental Table S1. Ethical approval was granted by the Dutch Central Committee on Research Involving Human Subjects (CCMO) and permission to use anonymised data from the TRAILS was granted by the study management committee.

Cohort members were assessed at baseline when aged 11 years (n=2230) and then at age 13 (n=2149), 16 (n=1816) and 19 years (n=1881). The retention rate over the 8-year follow-up period was 84.3% which is high for longitudinal studies of psychiatric outcomes (18, 19). TRAILS members lost due to attrition by age 19 were predominantly male from a lower socioeconomic background ($p<0.001$) but did not differ in terms of family functioning ($p=0.15$) or parental psychiatric history ($p=0.22$) from the rest of the cohort (19).

Instruments

Child Behaviour Checklist-Mania Scale (CBCL-MS) (20): Manic symptoms in the TRAILS cohort were captured using the CBCL-Mania Scale (CBCL-MS) which comprises 19 items selected from the CBCL (6-18) (21) to correspond to core and extended symptom domains for mania (Table 1 and Supplemental Table S2). The development and psychometric properties of the CBCL-MS are described elsewhere (20) and summarized in the supplemental material. We have previously shown that the CBCL-MS is a valid and reliable tool for assessing subclinical manic symptoms with improved discriminative ability for BD compared to other popular scales (20). In this analysis we used the standardized CBCL-MS scores of participants at age 11 years.

Computer Assisted Personal Interview version 20 (CAPI) of the Composite International Diagnostic Interview (CIDI): The CIDI is a comprehensive structured interview designed to be used by trained lay interviewers to yield diagnoses according to current classification systems (www.hcp.med.harvard.edu/wmhcdi). Lifetime disorders assessed in the CIDI included mood episodes and disorders (major depressive disorder [MDD], dysthymic disorder, mania, and hypomania), anxiety disorders (agoraphobia, generalized anxiety disorder [GAD], panic disorder, separation anxiety disorder, social phobia, and specific phobia), disruptive behavior disorders (oppositional defiant disorder [ODD] and conduct disorder [CD]), attention-deficit/hyperactivity disorder [ADHD], substance use disorders [SA] (alcohol abuse/dependence and drug abuse/dependence). CIDI assessments were conducted blind to participants' CBCL scores.

In this study, we considered lifetime diagnoses based on CIDI assessment of participants by age 19 years. We used a broad definition of Bipolar Disorder to include BDI, BDII, mania and hypomania. Unless otherwise specified we will use the term Bipolar Disorder (BD) when we refer to all four jointly. The CIDI has high test-retest reliability for the diagnosis of BDI (22) as well as excellent concordance rates with the Structured Clinical Interview for DSM-IV (SCID) for lifetime BDII and hypomania (23). Additional diagnoses considered were MDD, GAD and SA. This was based on previous evidence that subclinical manic states may also increase the risk for these disorders (11).

Wechsler Intelligence Scale for Children-Revised (WISC-R) (24): An estimate of intellectual ability was obtained at age 11 based on a composite measure derived from age-normalized standard scores of the Vocabulary and the Block Design subtests of the WISC-R.

General Functioning Subscale of the McMaster Family Assessment Device (FAD-GFS) (25): The FAD-GFS is a 12-item scale assessing six dimensions of family functioning; communications, problem solving, affective responsiveness, affective involvement, roles and behavior control. Total scores of 2 or above indicate family

dysfunction. In this analysis we used FAD-GFS data completed by the parents when participants were 11 years old.

Parental psychiatric morbidity: Participants' parents were first given a structured checklist of symptoms and disorders with detailed explanations and were asked to endorse those that applied. Subsequently trained interviewers asked follow-up questions to clarify the diagnostic significance of the reported symptoms and elicit details of treatment when applicable. In total, 45.5% of children had at least one parent with a psychiatric disorder (details in supplemental material). Although parental BD is a robust indicator of concordant offspring disorder (4, 9), we did not consider individual parental diagnoses as risk elevation is not confined to concordant disorders (26). Participants with at least one parent with any psychiatric diagnosis at baseline were considered positive for parental psychiatric morbidity.

Parental Socioeconomic status: Parental Socioeconomic Status (SES) at baseline was measured using a composite index of five indicators: maternal and paternal education, family income and maternal and paternal occupation, as defined by the International Standard Classification of Occupation (27). A composite index was constructed by averaging the five indicators upon standardization. This index was then used to specify three groups as low, moderate and high SES.

Statistical analysis

Latent Class Analysis was used to determine the number of underlying categories (latent classes) of participants needed to explain the pattern of associations between the 19 CBCL-MS items at age 11. IQ, parental SES, parental psychiatric morbidity and family function were also introduced in the model. We tested whether the data were explained by 1 to 4 classes with the option of testing further models if indicated. Multiple start values were considered for the estimated model parameters to avoid convergence on local, rather than global, solutions. Observing the same log likelihood obtained from multiple sets of start values increases confidence that the solution obtained is not a local maximum (28). Model fit was determined based on three

goodness of fit indices considered most robust: (a) the Bayesian Information Criterion (BIC); lower values indicate better fit to the data, (b) The Lo-Mendell-Rubin (LMR) likelihood ratio test of the hypothesis that a simpler model provides an equally good fit, and (c) the entropy of the model; higher entropy indicates that the latent classes are clearly distinguishable.

Upon identification of the best fitting model, we examined the effect of IQ, parental SES, parental psychiatric morbidity and family function based on their regression estimates on the latent variable representing class membership.

In order to ascertain the predictive value of class membership we used a series of logistic regression analyses to examine the association between class membership at age 11 and diagnoses of BD, MDD, GAD or SA between ages 12 to 19 years. Amongst the non-BD clinical outcomes, we focused on MDD, GAD and SA based on previous reports that subclinical manic states may increase the risk for these disorders as well (11). For these analysis the threshold of statistical significance was set to $p < 0.01$ following adjustment for multiple comparisons.

Finally, cox regression analysis was used to examine whether class membership was related to increased incidence rate for BD in addition to their potential association to increased cumulative likelihood of BD identified by logistic regression model.

All analyses were performed using MPlus 6.0 (www.statmodel.com) and IBM SPSS Statistics, Version 19 (www.spss.com).

Results

In total, 86 (5.4%) TRAILS participants were diagnosed with BD by age 19. Eleven had an established disorder at baseline and were therefore excluded from further analyses.

Classification of TRAILS participants at age 11 based on the CBCL-MS

The frequency of parental endorsement of each CBCL-MS item in the entire TRAILS sample is shown in Table 1. A 3-class solution provided the best model for explaining the association between CBCL-MS items as reflected in the BIC value, significant LMR p value (<0.0001) and higher entropy compared to the 1- and 2-class solutions (Table 2). The 4 and 5-class solutions had lower BIC values, but also lower entropy indicating worse fit (Table 2). Figure 1 presents the CBCL-MS item endorsement pattern in each of the 3 classes identified.

Class I ($n=862$; 45.2% of the cohort) included children whose parents endorsed on average 1.36 (1.15) CBCL-MS items. Since endorsement was minimal we consider this an “asymptomatic class”. This is also confirmed by the low rates of disruptive disorders within this class, mainly ODD (2.1%), CD (1.5%) and ADHD (1.1%). Class II ($n=845$; 44.3% of the cohort) included children whose parents endorsed on average 5.76 (1.89) CBCL-MS items. Their mean standardized CBCL-MS total score was 53.01 (4.80). A small proportion of children in this class (11.1%) had been diagnosed with disruptive disorders by age 11, mainly ODD (4.4%), CD (4.2%), and ADHD (4.1%). We considered this a “mildly symptomatic class”. Class III ($n=199$; 10.4% of the cohort) included children whose parents endorsed 10.37 (2.07) CBCL-MS items. Their mean standardized CBCL-MS total score was 71.40 (7.34). Additionally, 27.2% of children in this class had been diagnosed with disruptive disorders by age 11, particularly ADHD (14.0%), ODD (13.1%) and CD (7.0%). Therefore we considered this a “highly symptomatic class”.

Association of class membership with demographic and risk factors

IQ, SES, family dysfunction and parental psychiatric morbidity were significantly associated with class membership. Children in the highly symptomatic class were significantly more likely to have lower IQ, lower parental SES, greater family dysfunction and positive parental psychiatric morbidity compared to the other two classes (Table 3 and Figure 2). The male to female ratio was nearly equal in the mildly symptomatic class (1.0:0.9). However, females were overrepresented in the asymptomatic class (1.0:1.5) and underrepresented in highly symptomatic class (1.0:0.5).

Class membership at age 11 and risk for subsequent BD

Of the 69 TRAILS participants diagnosed with BD between 12 and 19 years, 14 (1.6%) derived from the asymptomatic class, 33 (3.9%) from the mildly symptomatic class and 15 (7.5%) from the highly symptomatic class (supplemental Table S3). Class membership at age 11 was significantly associated with subsequent diagnosis of BD ($\chi^2=25.54$, $p<0.001$); referenced to the asymptomatic class, the odds ratio (OR) for BD by age 19 was 2.66 (95%CI 1.41-5.02) in the mildly symptomatic class and 7.1 in the highly symptomatic class (95% CI 3.32-15.11). The association between class membership and BD was 3.5-fold higher for females (OR=13.42, 95%CI 4.60-39.18) than males (OR=3.8, 95% CI 1.29-11.22).

Estimated Hazard Ratios (HR), referenced to the asymptomatic class, were 2.61 (95% CI 1.40-4.87) for the mildly symptomatic class and 6.58 (95% CI 3.18-13.63) for the highly symptomatic class. ORs reflect the cumulative increase in the likelihood of BD while HRs reflect the increase in the incidence rate of BD in the mildly and highly symptomatic class. The similarity between the ORs and the HRs might be partially explained by the small number of cases presenting with BD; yet it affirms the robustness of the association between class membership and risk for BD as it indicates that this association remains significant throughout the follow-up period.

Class membership at age 11 and risk for subsequent non-BD disorders

The lifetime prevalence of MDD, GAD and SA by age 19 years was 15.7% (n=248), 4.0% (n=64) and 29.9% (n=473) respectively. As shown in Figure 3, class membership did not predict MDD ($\chi^2=2.64$, $p=0.27$) or GAD ($\chi^2=3.05$, $p=0.22$). Membership of the mildly, but not the highly, symptomatic class was associated with SA ($\chi^2=12.40$, $p=0.05$) although below the corrected statistical threshold.

Alarm Symptoms for BD

Parental endorsement of CBCL-MS items in the asymptomatic class was negligible. In the mildly symptomatic class, parents endorsed on average 5 CBCL-MS items but none with a probability higher than 0.1 (Figure 1). In contrast, the highly symptomatic class was characterized by a clustering of CBCL-MS items of hyperactivity, impulsivity, clowning, reduced sleep, mood lability and increased and loud speech that were endorsed with a probability of ≥ 0.3 (Figure 1) resulting in standardized CBCL-MS total score ≥ 70 . This score corresponds to the lower limit of the 95% CI for CBCL-MS scores of the highly symptomatic class.

An important metric in considering this cluster as “alarm symptoms” is their positive and negative predictive value for BD. Positive predictive value (PPV) is the proportion of those with “alarm symptoms” who actually develop BD. Negative predictive value (NPV) is the proportion of those without “alarm symptoms” who do not develop BD. The PPV and NPV of the “alarm symptoms” identified here was 13.2% and 96.3% respectively thus conforming to conventional values for “alarm symptoms in medicine” (16).

Discussion

We show that it is possible to define subclinical manic symptoms in childhood that conform to the concept of “alarm symptoms” as they allow classification of individuals according to their risk of subsequent syndromal BD.

Empirically derived classification based on degree and pattern of manic symptoms

Consistent with previous reports we found that subclinical manic symptoms were common in childhood (Table 1) (11, 12). The pattern and degree of these symptoms could be best explained by a 3-class model. In the asymptomatic class there was minimal parental endorsement of any CBCL-MS item. At the other end, the highly symptomatic class was characterized by parental endorsement of most CBCL-MS items with the highest probability of endorsement (≥ 0.3) observed for items reflecting hyperactivity, impulsivity, inattention, mood lability, increased volume and amount of speech and reduced sleep. Previous studies have also identified this clustering of symptoms as a dimension of subclinical manic states (29).

A large proportion (27.2%) of children in the highly symptomatic class had childhood diagnoses of disruptive behavior disorders. This confirms previous reports that highly deviant subclinical manic states are associated with high rates of psychiatric disorders, particularly ADHD (29). It would appear that behavioral measures and risk factors, even when considered together, do not allow sufficient separation between ADHD and childhood antecedents of BD. This suggests that either the two disorders have overlapping pathophysiology or that measures with greater biological specificity are needed to differentiate them (30).

Implications for the early detection of Bipolar Disorder

Our results lend direct empirical support to the recent proposal by Post et al (2013)(31) that clinical features associated with high risk for BD could be used to formulate prevention strategies pending more detailed biological validation. The PPV and NPV of the “alarm symptoms” identified here was 13.2% and 96.3% respectively.

The high NPV suggests that only about 3 out of 100 people without “alarm symptoms” will develop BD. Therefore in the absence of “alarm symptoms” subsequent BD is highly unlikely even when risk factors are present. The PPV of 13.2% suggests that about 13 out of 100 individuals with “alarm symptoms” will develop BD. By way of comparison, the PPV of “alarm symptoms” for cancer in community samples usually ranges between 2-10% (16, 32-34; Supplemental material). The PPV of any test depends on the prevalence of the disease in the population. Experience from oncology has shown that relatively low values are statistically inevitable when clinical features alone are used for disorders with low population prevalence (34). It is therefore acknowledged that although “alarm symptoms” occur in the minority of patients who eventually develop cancer their presence requires further investigation. Acting on “alarm symptoms” for cancer has also been shown to assist in the early diagnosis of non-malignant disorders (35). Based on the UK primary care database, which holds information on 762325 individuals aged 15 or older assessed between 1994-2000, for every 4-7 patients investigated for “alarm symptoms” for cancer one was found to have another non-malignant but clinically important disorder requiring further intervention (35). A similar case could be made for the “alarm symptoms” for BD as identified here. Although the presence of “alarm symptoms” for BD did not confer higher risk of MDD, GAD and SA, 62 individuals (30%) presenting with “alarm symptoms” had such non-BD diagnoses by age 19. This does not diminish the importance of “alarm symptoms” for BD but reinforces their usefulness from a public health perspective.

In the field of psychiatry we are beginning to engage in a public dialogue about the management of early signs of mental illness (36). “Alarm symptoms” as identified here are not diagnostic but allow the initiation of a meaningful discussion between parents and clinicians about further management. These initial steps would need to be formally evaluated in terms of effectiveness but in principle they should include education, vigilance and risk minimization. In the context of our specific findings risk

minimization could focus on identifying and treating parental psychiatric disorders and improving family function.

Methodological considerations

A particular strength of this study is the availability of data from a representative population sample of young where manic symptoms were captured contemporaneously and are free from recall or attribution biases. A further strength relates to case ascertainment which was not influenced by sampling biases associated with help-seeking behavior, impairment or symptom severity. Previous studies have shown that the severity of subclinical manic states is associated with greater functional impairment (12,13, 29) but there is little evidence to suggest that impairment is predictive of conversion (13). The prevalence of BD in this sample was consistent with that reported in other general population studies which support the generalizability of our findings (37). Although the CIDI is widely used, its structured format and administration by lay interviewers may limit the amount of information elicited. Data regarding syndromal conversion were available up to age 19 years. This could have led to an under-estimation of the PPV as the cohort had not yet passed the entire period of risk and it is possible that further cases of BD may present in the future. The scale used here does not allow us to comment on the contribution of episodicity. Episodicity is considered a salient clinical feature of BD particularly when assessing young people (38). It has been suggested that conversion to syndromal BD is increased in youth with episodic manic symptoms (39) but not in those with more chronic presentations (40). It is therefore possible that the addition of information of episodicity may further refine “alarm symptoms” for BD.

Conclusions

Our results provide support for the concept of “alarm symptoms”, symptoms that are associated with a subsequently greatly elevated risk of BD. More research using well-characterized large populations, from different settings, should further refine the

concept of “alarm symptoms” and determine investigations and interventions to be pursued.

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Table 1. Frequency of endorsement of Child Behavioral Checklist-Mania Scale (CBCL-MS) at age 11 years

CBCL –MS Items	Frequency of Endorsement in the TRAILS (%)
Inattentive or easily distracted	45.9
Impulsive or acts without thinking	44.9
Can't sit still, restless or hyperactive	41.4
Talks too much	39.5
Feels others are out to get him/her	30.4
Showing off or clowning	29.6
Unusually loud	29.4
Sudden changes in mood or feelings	27.7
Teases a lot	26.0
Sleeps less than most kids	23.6
Trouble sleeping	15.6
Gets in many fights	13.5
Suspicious	13.4
Thinks about sex too much	4.7
Strange ideas	4.5
Sees things that aren't there	3.1
Hears sound or voices that aren't there	2.9
Plays with own sex parts too much	2.6
Plays with own sex parts in public	1.5

Table 2. Fit Indices for 1-5 Latent Class Solutions

	BIC	AIC	SSA-BIC	Entropy	LMR p value
1 Class	41063.10	40851.09	40942.38		
2 Classes	36194.22	35744.41	35936.89	0.83	<0.0001
3 Classes	35402.25	34713.64	35008.30	0.84	<0.0001
4 Classes	35396.68	34469.28	34866.12	0.80	0.002
5 Classes	35519.03	34352.84	34851.85	0.76	0.76

BIC=Bayesian Information Criterion; AIC=Akaike Information Criterion; LMR=Lo-Mendell-Rubin; SSA-BIC=Sample Size adjusted BIC

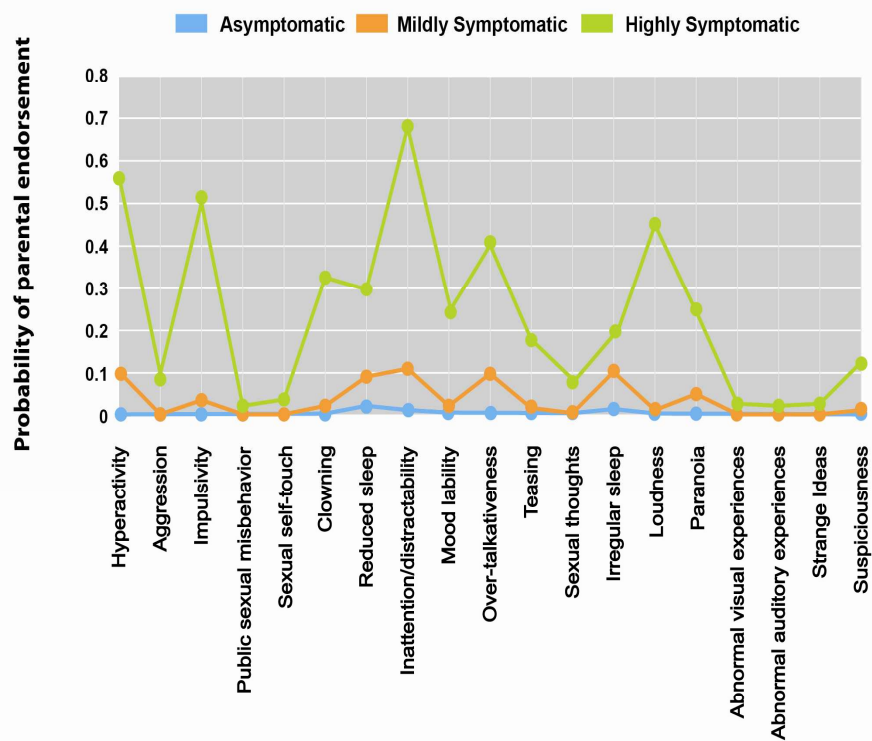
Table 3. Effect of covariates on class membership

	Asymptomatic vs. Mildly symptomatic Class			Asymptomatic vs. Highly Symptomatic Class			Mildly vs. Highly Symptomatic Class		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Lower parental SES	0.73	0.64- 0.84	<.001	0.59	0.47-0.75	<.001	0.77	0.60- 0.99	0.04
Lower IQ	0.99	0.98-0.99	<0.001	0.97	0.96-0.98	<.001	0.98	0.97- 0.99	0.002
Family Dysfunction	2.79	2.08-3.74	<.001	8.50	5.14- 14.06	<.001	3.07	1.91- 4.95	<.001
Parental Psychiatric Morbidity	1.41	1.15-1.72	.001	2.53	1.80-3.56	<.001	1.80	1.30- 2.50	<.001

SES=socioeconomic status; Family Dysfunction as assessed with the General Functioning Subscale of the McMaster Family Assessment Device

Figures

Figure 1. Child Behaviour Checklist-Mania Scale (CBCL-MS)



CBCL-MS items corresponding, from left to right, to item numbers
10, 37, 41, 59, 60, 74, 76, 78, 87, 93, 94, 96, 100, 104, 34, 70, 40, 85, 89, in the CBCL 6/18
Also in Table 1

Figure 2. Cognitive, Socioeconomic and Family Characteristics of the Asymptomatic, Mildly Symptomatic and Highly Symptomatic Classes

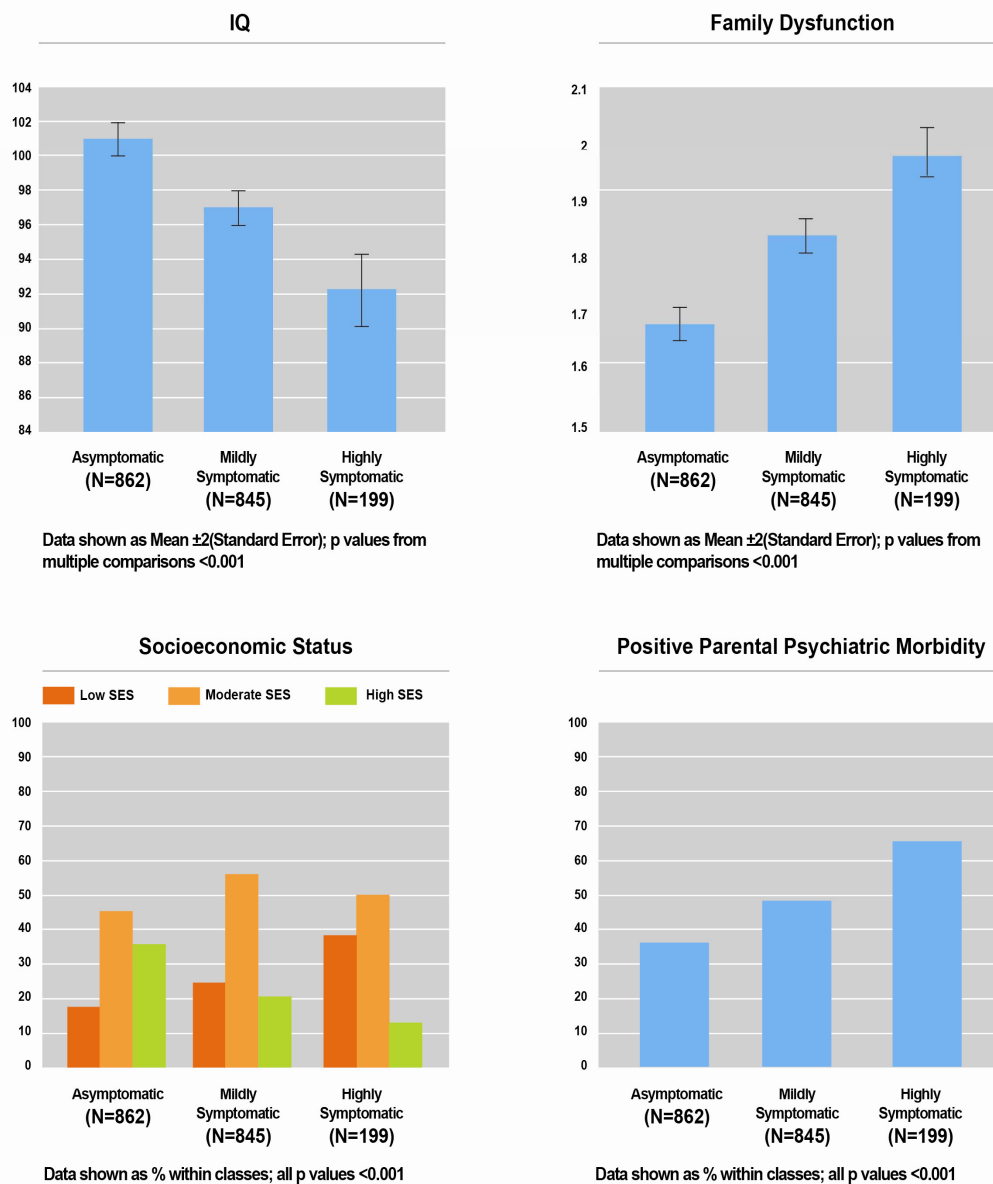
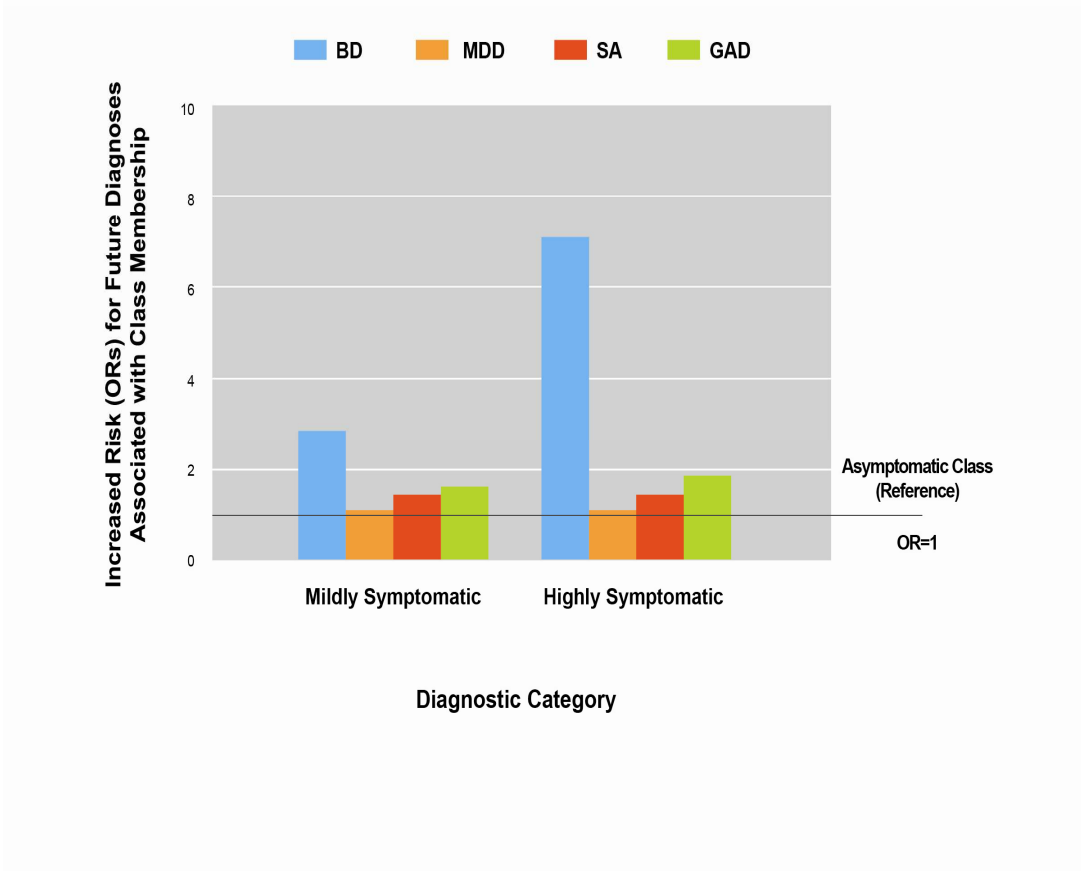


Figure 3. Specificity of the association of class membership to syndromal BD



Supplemental Material

A. Representativeness of the TRAILS sample

The TRAILS cohort was identified through birth and school registers in the 5 northern municipalities of Holland. The TRAILS cohort was identified through birth and school registers. Recruitment was based on entire schools participating; 91% of all the schools in the municipalities agreed to take part. Data collection began when participants were aged 11 years. According to the TRAILS data collection protocol, information was obtained on participants' general intellectual ability, parental socioeconomic status and psychiatric morbidity and family functioning. Behavioral assessments were undertaken at age 11, 13 and 16 years and formal lifetime psychiatric diagnoses were ascertained at age 19 years. All data were anonymised by TNS NIPO (www.tns-nipo.com), a custom research company. Table S1 shows that key variables regarding representativeness of the TRAILS cohort are comparable to those from the 2001 Dutch national census.

Table S1. Characteristics of TRAILS participants at enrolment compared to the 2001 national census data available online from the Centraal Bureau voor de Statistiek (www.cbs.nl)		
	TRAILS	2001 Dutch Census
% Girls	50.8%	48.8% ¹
% White European	89.4%	93.2% ¹
Lower parental education ²	32.6%	30.6%
% children living with both parents ³	84.5%	84%
Median disposable household income	21780 Euros	20700 Euros
¹ The census reported on the 10-15 years age range; ² Defined as having completed up to lower half of secondary school; ³ includes married and cohabiting couples		

B. Development of the Child Behaviour Checklist-Mania Scale (full details in Papachristou et al. PloS ONE 2013)

We followed a typical content validity procedure (Grant & Davis, 1997; Lengua et al, 2001) which involves content experts who judge each item of an instrument against the definition of the domains intended to measure and score its relevance on a 4-point scale ranging from 1 (irrelevant) to 4 (highly relevant). In our study, content validity was assessed by a panel of 10 qualified child and adolescent psychiatrists (average number of years of clinical and research experience: 8; range: 4—20 years).

These experts were representative of the professional settings (inpatient, outpatient, academic) within the South London and Maudsley NHS Foundation Trust. They rated the relevance of each item from the total item pool of the CBCL 6-18 on a scale of 1-4 against each of the symptom domains that correspond to operational criteria for mania of both the Diagnostic Statistical Manual for Mental Disorders (www.dsm-5.org) and the International Classification of Diseases (www.who.int/classifications/icd). In addition, the panel considered CBCL items relating to psychotic-like experiences as childhood and adolescent. Our decision was largely based on data suggesting that psychotic symptoms are strongly associated with BD (OR=14.8; 95%CI 8.7-25.2) (van Os et al., 2000) and that psychosis prone individuals are much more likely (29% vs 5%) to develop BD (Verdoux & van Os, 2002). The content validity index (CVI) for each item was established by calculating the proportion of experts scored it as relevant (score 3) or highly relevant (score 4) for any of the domains. A minimum item CVI of 0.80 (Grant & Davis, 1997) was required for inclusion in the second stage where final item inclusion to the CBCL-MS was based on unanimous agreement. Following consensus meetings, 19 items were selected for inclusion in the CBCL- Mania Scale (CBCL-MS) (Supplemental Table S2). The scoring of the CBCL-MS at each assessment age was based on summing the scores of each of the 19 individual items. Scores were then standardized (T scores) following the scoring procedure recommended by Achenbach and Rescorla (2001) using the TRAILS data as the standardization sample. Standardization of the CBCL scores for the CBCL-MS, as well as for other CBCL-based syndrome scales, was performed separately for each wave.

Table S2. Child Behavior Checklist-Mania Scale items and corresponding core and extended criteria for Mania

CBCL Items	DSM criteria for Mania
Core Symptoms	
37. Gets in many fights	A distinct period of abnormally and persistently elevated, expansive or irritable mood
87. Sudden changes in mood or feelings	
96. Thinks about sex too much	
74. Showing off or clowning	Inflated self-esteem or grandiosity
94. Teases a lot	
76. Sleeps less than most kids	Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
100. Trouble sleeping	
93. Talks too much	More talkative than usual or pressure to keep talking
104. Unusually loud	
	Flight of ideas or subjective experience that thoughts are racing
78. Inattentive or easily distracted	Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
10. Can't sit still, restless or hyperactive	Increase in goal-directed activity (at work, at school, or sexually) or psychomotor agitation
60. Plays with own sex parts too much	
41. Impulsive or acts without thinking	Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
59. Plays with own sex parts in public	
Extended Symptoms	
34. Feels others are out to get him/her	Delusions
85. Strange ideas	
89. Suspicious	
40. Hears sound or voices that aren't there	Hallucinations
70. Sees things that aren't there	
Items numbers correspond to those in the Child Behaviour Checklist (6/18)	

Reliability analysis demonstrated high internal consistency for the 19 items of the CBCL-MS at all assessment ages (Cronbach's $\alpha \geq .80$; total item correlation $> .37$). Based on Receiver Operator Curve (ROC) analysis on the CBCL-MS data the area under the curve (AUC) was 0.64 ($p < .01$) which represents a satisfactory performance for a general population sample. A forward stepwise logistic regression model showed that the CBCL-MS had significantly increased ability to predict BD compared to the CBCL-Pediatric Bipolar Disorder scale (Wald $\chi^2 = 12.69$, $p < .001$) and the CBCL-Externalizing Scale (Wald $\chi^2 = 3.47$, $p = .05$).

C. Details of Parental Morbidity in the TRAILS Sample

Table S3. Parental Psychiatric Morbidity in the TRAILS sample		
Diagnosis	Percentage (%) of children in the TRAILS sample per parental diagnosis	
	Paternal	Maternal
Bipolar Disorder	3.5	5.8
Major Depressive Disorder	16.0	27.0
Any Anxiety Disorder	5.3	15.1
Schizophrenia and spectrum disorders	1.9	2.1
Substance Abuse (includes drugs and alcohol)	6.4	2.1
Other	6.8	6.9

D. Characteristics of patients with Bipolar Disorder per class

Table S4. Characteristics of cases with syndromal BD by age 19 according to class membership at age 11

	BD cases arising from the Asymptomatic Class (N=14)	BD cases arising from the Mildly Symptomatic Class (N=33)	BD cases arising from the Highly Symptomatic Class (N=15)
% of all cases with Bipolar Disorder in the TRAILS sample	16.2	38.37	17.4
Male: Female ^a	1.0:1.0	1.0:0.7	1.0:1.1
% High SES ^b	35.3	52.9	11.8
IQ ^c	98.29 (14.06)	95.18 (12.30)	97.40 (14.25)
% Parental Psychiatric Morbidity ^d	15.6	53.1	31.2
Age of Onset of BD (years) ^e	15.57 (2.06)	15.45 (2.33)	15.67 (2.22)
% Previously Diagnosed with Disruptive Behaviour Disorders ^f	11.8	52.9	35.3
Continuous data are presented as mean (standard deviation); Categorical data are presented as proportions (%) across classes; ^a $\chi^2=0.57$, $p=0.75$; ^b $\chi^2=3.84$, $p=0.43$ ^c $F_{(2,59)}=0.33$, $p=0.72$; ^d $\chi^2=2.78$, $p=0.25$; ^e $F_{(2,59)}=0.05$, $p=0.95$; ^f $\chi^2=2.40$, $p=0.30$			

E. Positive Predictive Value of “Alarm Symptoms” for Cancer

Table S5. Positive Predictive Value of “Alarm Symptoms” for Cancer

Alarm Symptoms	Positive Predictive Value
Rectal examination for prostate malignancy ¹	12%
Hematuria for urological cancer ^{2,3}	7-10%
Fecal occult blood for colon cancer ^{1, 3}	2-6%
Dysphagia for gastrointestinal cancer ^{2,3}	2-7%
Hemoptysis for lung cancer ^{3,4}	5-7%
Concomitant presence of haemoptysis, loss of weight, loss of appetite, dyspnoea, thoracic pain, fatigue and cough for lung cancer ⁴	10%
Values cited are averages or pooled estimates from primary care or community samples; ¹ Shapley et al. Br J Gen Pract 2010; ² Bruyninckx et al. Br J Gen Pract 2003; ³ Jones et al. BMJ 2007; ⁴ Hamilton et al. Thorax 2005	

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6 Trajectories to Bipolar Disorder from Childhood to Adulthood

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Trajectories to Bipolar Disorder from childhood to adulthood

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Abstract

Importance: There are unresolved questions regarding the early natural history of Bipolar Disorder (BD). Prospective longitudinal studies are needed to determine the dynamic course of subclinical manic states and their predictive validity for syndromal onset of BD.

Objectives: To chart the trajectories of subclinical manic states throughout adolescence and their relationship to conversion to syndromal BD.

Design: Prospective multi-wave 8-year follow-up study

Setting: European general population cohort

Participants: Participants of the TRacking Adolescents' Individual Lives Survey (TRAILS) assessed at baseline aged 11 years (n=2230) and then at age 13 (n=2149), 16 (n=1816) and 19 years (n=1881).

Main Outcomes and Measures: Growth Curve Model estimated trajectories of subclinical manic states for TRAILS participants classified as asymptomatic, mildly symptomatic and highly symptomatic based on their score on the Child Behaviour Checklist-Mania Scale at age 11. Lifetime diagnoses of BD by age 19 years were ascertained using the Composite International Diagnostic Interview.

Results: In the asymptomatic class, both converters and non-converters showed an increase in CBCL-MS total and factor scores between assessment wave 1 and 3. The mean change and the mean rate of change were greater for converters. In the mildly symptomatic class both converters and non-converters followed similar trajectories of decreasing in CBCL-MS scores. In the highly symptomatic class, the trajectories of converters and non-converters diverged significantly. Non-converters showed progressive decrease in psychopathology while converters evidenced persistence (but no exacerbation) of subclinical manic symptoms. We found no evidence of symptomatic exacerbation within the year preceding syndromal onset of BD.

Conclusions and relevance: Our findings reconcile previous conflicting views regarding the early natural history of BD and suggest that the degree and pattern of childhood subclinical manic states remains a key predictor of subsequent BD.

Introduction

The diagnosis and clinical subtyping of Bipolar Disorder (BD) depend on the severity and duration of manic symptoms. Adolescence and young adulthood are peak periods of risk for the syndromal onset of BD.¹⁻³ Therefore there is much clinical and public health interest in the predictive value of subclinical manic symptoms in youth as they may signal the onset of syndromal BD.

Careful follow-back studies clearly indicate that the majority (up to 50%) of patients with BD report subclinical symptoms that predate syndromal onset by an average of 7 years.⁴⁻¹¹ Approximately 70% of patients experience subclinical manic symptoms of elation/irritability, reduced sleep, impulsivity and increased speech.⁶⁻¹¹ Depressive symptoms are also common but less prevalent.⁶⁻¹¹ Follow-up studies of offspring of BD offer a prospective evaluation of the temporal evolution of subclinical symptoms preceding and leading to the onset of BD.¹²⁻¹⁵ These studies describe premorbid depressive and anxious symptomatology in the early childhood of high-risk individuals.¹²⁻¹⁵ In those later developed BD manic symptoms become more clearly defined during adolescence.^{13,14} Taken together this evidence has been used to argue that subclinical manic symptoms may define prodrome-like mental state for BD.¹⁶⁻¹⁸ At the same time it is acknowledged that recall and attribution biases or the presence of parental disorder pose significant limitations and challenges to the generalisation of retrospective and high risk studies.^{16,17} Prospective examination of general population samples of youth are particularly useful in addressing these concerns. Informative studies that used repeated assessments over follow-up periods of 10-16 years are the Oregon Adolescent Depression Project,¹⁹ the Dunedin Multidisciplinary Health and Development Study (Kim-Cohen et al. 2003),²⁰ and the Early Developmental Stages of Psychopathology study.²¹⁻²³ These studies demonstrate that manic symptoms, particularly during adolescence, in the general population are both highly prevalent and weakly predictive of clinical outcomes.¹⁹⁻²³ At any time, about 40% of youth may express at least one and approximately 10% may manifest more than 7 manic symptoms.²¹⁻²³ A more recent investigation of the early antecedents of BD from our group suggests

that it is possible to enhance the predictive validity of manic symptoms by focusing on the profile (number, type and severity) of manic symptoms in childhood.²⁴

We used data from the TRacking Adolescents' Individual Lives Survey (TRAILS) (www.trails.nl), a four-wave study of a representative cohort of 2230 Dutch children born between 1 October 1989 and 30 September 1991 in the northern Netherlands.²⁵⁻²⁷ Participants were first assessed at age 11 years (wave-1) and then at age 13, 16 and 19 years. We used the Child Behaviour Checklist-Mania Scale (CBCL-MS) (details in Supplement),²⁸ which records parental endorsement of 19 manic behaviours, to define subclinical manic states from childhood (wave-1) to adolescence (wave-3). At age 11, manic symptoms clustered in four factors corresponding to distractibility/disinhibition, psychosis, increased libido and disrupted sleep (Figure 1). It is important to note that this factor structure remained very stable over the three assessment waves (details in Supplement).²⁸ Using the CBCL-MS symptom profile at age 11 latent class analysis stratified the TRAILS sample into an asymptomatic, mildly symptomatic and highly symptomatic class (Table 1).²⁴ The lifetime prevalence of broadly defined BD by age 19 years in each class was 2.1%, 5.4% and 13.2% respectively. Compared to the asymptomatic class, the odds ratios for future BD in the mildly and highly symptomatic classes were 2.7 (95% CI 1.41-5.01) and 7.1 (95% CI 3.31-15.11) respectively. The positive and negative predictive value of class membership was 13.2% and 96.3% respectively. These results established that subclinical manic states in childhood are predictive of future risk for BD.^{24,28}

The present analysis examines the trajectories of subclinical manic states, captured by the CBCL-MS, throughout the period of adolescence for individuals in each class. In addition to the total CBCL- MS score, we also examine longitudinal change in the factors of distractibility/inattention, psychosis, increased libido and disrupted sleep as these dimensions of subclinical manic states may follow different trajectories. We test whether longitudinal changes in subclinical manic states or specific symptom dimensions can differentiate TRAILS participants who convert to BD by age 19 years (converters) from those who do not (non-converters) within each class.

Methods

Participants and Procedures

Details of the TRAILS design, sampling and assessments have been published elsewhere²⁵⁻²⁷ and are summarised in the Supplement and eTable 1. The cohort comprises 2230 individuals born in the northern Netherlands between 1 October 1989 and 30 September 1991. Cohort members were assessed at baseline when aged 11 years (n=2230) and then at age 13 (n=2149), 16 (n=1816) and 19 years (n=1881). The retention rate over the 8 year follow-up period was 84.3% which is high for longitudinal studies of psychiatric outcomes.^{25,26} Behavioral assessments were undertaken at age 11, 13 and 16 years and formal lifetime psychiatric diagnoses were ascertained at age 19 years. TRAILS members lost due to attrition at age 19 were predominantly males from a lower socioeconomic background ($p<0.001$) but did not differ in terms of family functioning ($p=0.15$) or parental psychiatric history ($p=0.22$) from those who participated at baseline.²³ Ethical approval was granted by the Dutch Central Committee on Research Involving Human Subjects and permission to use anonymised data from the TRAILS was granted by the study management committee.

Behavioral assessments at age 11, 13, and 16 years were based on the Child Behavioral Checklist-Mania Scale (CBCL-MS).²⁷ The scale records parental endorsement of 19 items capturing the presence of subclinical manic symptoms over the previous 6 months (see eTable 2). Reliability analysis demonstrated high internal consistency for the 19 items of the CBCL-MS (Cronbach's $\alpha \geq 0.80$; total item correlation >0.37). Principal component analyses (PCA) of the CBCL-MS data at ages 11, 13 and 16 years resulted in an almost identical factor structure and explained 48.18%, 46.06% and 44.94% of the variance of the items respectively. The four factors corresponded to: (1) distractibility/ disinhibition (2) psychosis (3) increased libido (4) disrupted sleep (details in Supplement and eTables3-4). Confirmatory Factor Analyses established good fit of the data; Root Mean Square Error of Approximation values were 0.04, 0.04 and 0.05, and Confirmatory Fit index values were 0.97, 0.96 and 0.92 for the three assessment waves respectively.

At age 19, lifetime diagnoses of TRAILS participants were ascertained using the Computer Assisted Personal Interview, version 20, of the Composite International Diagnostic Interview (CIDI) (www.hcp.med.harvard.edu/wmh/cidi). Diagnostic assessments were conducted blind to participants CBCL scores. In this study, we considered lifetime diagnoses of broadly defined Bipolar Disorder to encompass BDI, BDII, mania and hypomania. The CIDI has high test-retest reliability for the diagnosis of BDI²⁸ as well as excellent concordance rates with the Structured Clinical Interview for DSM-IV (SCID) for lifetime BDII and hypomania.²⁹

Classification of TRAILS participants based on the CBCL-MS at age 11 years

As we have previously reported²³ latent class analysis of the CBCL-MS total score at age 11 year identified three classes of TRAILS participants as shown in Table 1 (also eTable 6). The probability of parental endorsement of CBCL-MS items at age 11 for each class is shown at Table 2. In the asymptomatic class there was minimal parental endorsement of any CBCL-MS item. In the mildly symptomatic class, parents endorsed on average 5 symptoms but none with a probability of more than 0.1. By contrast, parents in the highly symptomatic class endorsed on average 10 symptoms. The highest probability of endorsement (≥ 0.3) was observed for items reflecting hyperactivity, impulsivity, inattention, mood lability, increased volume and amount of speech and reduced sleep.

TRAILS participants in the highly symptomatic class were significantly more likely to have lower IQ, lower parental SES, greater family dysfunction and positive parental psychiatric morbidity compared to the other two classes (Table 1). Class membership at age 11 was significantly associated with subsequent diagnosis of BD ($\chi^2=25.54$, $p<0.001$) but not of depression, anxiety or substance abuse disorder ($p>0.05$); referenced to the asymptomatic class, the odds ratio for BD by age 19 was 2.66 (95%CI 1.41-5.02) in the mildly symptomatic class and 7.1 in the highly symptomatic class (95% CI 3.32-15.11). Of the 69 TRAILS participants who converted to syndromal BD between 12 and 19 years, 14 (1.6%) derived from the asymptomatic class, 33 (3.9%) from the mildly symptomatic class and 15 (7.5%) from the highly symptomatic class (Table 1).

Statistical analysis

Within each class, Growth Curve Models (GCMs) were fitted to examine potential differences in the longitudinal evolution of CBCL-MS total and factor scores between youths who converted to BD by age 19 years and those who did not. Since conversion to BD could have occurred at any time during the 8-year follow-up period, missing values to CBCL-MS scores were assigned for future assessments of those participants who converted to BD between assessment waves. These participants were compared with the remaining participants for differences in their CBCL-MS scores in the assessments preceding onset. As all tests examining these differences yielded non-significant results (all p values >0.05), the assigned missing data were assumed to be missing Completely at Random (MCAR). Under the MCAR assumption, we used full information maximum likelihood to estimate the trajectories of all cases across the three assessment waves conditional on observed trajectories.

For each model, goodness of fit was determined based on the normed chi square and the comparative fit index, which are considered less sensitive to sample size.^{30,31} The normed chi square (χ^2 divided by the degrees of freedom of the model) tests the hypothesis the covariance matrix predicted by the model does not differ from the observed covariance matrix. Therefore the model is acceptable if the normed χ^2 is less than 5.³² The Comparative Fit Index (CFI) compares the fit of the covariance matrix predicted by the model to an independent model which assumes that the variables are uncorrelated. The predicted model is considered acceptable if the CFI exceeds 0.90.³⁰ Given an acceptable model fit, we considered the models' intercept, which represents CBCL-MS total or factor scores at baseline, and slope, which represents the rate of change across assessment waves. Positive or negative slope values respectively reflect increases or decreases in the rate of change. Significant values ($p < 0.05$) for the slope indicate the presence of intra-individual change over time. Significant p values ($p < 0.05$) for the variance estimates of the intercept and slope, indicate significant inter-individual differences in baseline and rate of change over time.

Since the interval between the last CBCL-MS assessment and syndromal conversion to BD was variable we conducted a further GCM analysis which was

restricted to cases who had converted within 1 year of their last behavioral assessment irrespective of class. This allowed us to comment on whether there were significant changes in CBCL-MS total or factor scores proximal to disease onset.

Analyses were performed using MPlus 6.0 (www.statmodel.com) and IBM SPSS Statistics, Version 19 (www.spss.com).

Results

For all models tested, the normed chi-square was < 3.97 and the CFI was > 0.93 suggesting good model fit. Threshold for statistical inference was set at $p < 0.001$. We focus on changes in the CBCL-MS total score. Results for the CBCL-MS factor scores will be presented only when they differed from those of the total score.

Asymptomatic Class

For the non-converters, the mean intercept for the CBCL-MS total score was 42.13 ($p < 0.001$). The mean slope was 1.85 ($p < 0.001$); the mean slope having a positive value is consistent with increased intra-individual CBCL-MS score over time. On average, the increase was 3.7 points between assessment waves 1-3 (Figure 2). The variance of the intercept and the slope were also significant indicating significant inter-individual variability. Analysis of the CBCL-MS factor scores showed that they followed the same direction and pattern as the CBCL-MS total score.

For converters, the mean intercept of the CBCL-MS total score was 42.4 ($p < 0.001$). The mean slope was 3.14 ($p = 0.004$) indicating significant intra-individual increase over time. On average, the increase in the CBCL-MS total score was 6.2 points between assessment waves 1-3 (Figure 2). The variance of the intercept and slope was not significant indicating minimal inter-individual variability.

Mildly Symptomatic Class

For non-converters, the mean intercept and slope values for the CBCL-MS total score were 52.95 ($p < 0.001$) and -0.63 ($p = 0.002$) respectively. The negative slope value indicates intra-individual decreased in CBCL-MS total score over time. On

average, the CBCL-MS total score decreased by 1.2 points between assessment waves 1-3. The variance estimates for the mean intercept was significant for the CBCL-MS total and factor scores. The variance estimates for the slope was significant for the CBCL-MS total and the Distraction/Disinhibition factor score but not for the remaining CBCL-MS factor scores (all $p > 0.12$).

For converters, the mean intercept and the mean slope values for the CBCL-MS total scores were 54.87 ($p < 0.001$) and -2.67 ($p < 0.001$) respectively. On average, the CBCL-MS total scores decreased by 5.3 points between assessment waves 1-3 (Figure 2). The variance estimates for the intercept was also significant. The variance estimates for the slope was significant for the CBCL-MS total and the Distraction/Disinhibition factor score but not for the remaining CBCL-MS factor scores (all $p > 0.46$).

The mean slopes of non-converters and converters were not significantly different suggesting that the trajectories of the two groups were comparable.

Highly Symptomatic Class

For non-converters, the mean intercept and slope of the CBCL-MS total score were 71.07 ($p < 0.001$) and -3.45 ($p < 0.001$). Non-converters showed an average decrease of 6.9 points between assessment waves 1-3 (Figure 2). The variance of the intercept and slope were not significant for the CBCL-MS total score. For the Psychosis and Disrupted Sleep factors, the mean and variance of the intercepts were significant but the slopes were not.

For converters, the mean intercept of the CBCL-MS total score was 72.49 ($p < 0.001$). However the mean slope was not significant ($p = 0.33$) indicating minimal change over time. The same pattern for mean intercepts and slopes was observed for the CBCL-MS factor scores; none of the slopes were significant ($p > 0.32$).

The mean slopes of non-converters and converters were significant suggesting that non-converters had a different trajectory marked by decreasing psychopathology while no change was noticeable for converters.

CBCL-MS changes proximal to syndromal onset of BD irrespective of class

In order to control for the variable interval between age at the last behavioral assessment and age at syndromal onset of BD we conducted an additional GCM examining the trajectories of CBCL-MS scores for participants ($n=20$) who were diagnosed with syndromal BD, irrespective of class, within a year of their last behavioral assessment. Model fit to the data was excellent (normed chi-square=0.44, CFI>0.95). The mean intercept and variance of the intercept were both significant, indicating inter-individual heterogeneity. However, the slope was not significant ($p=0.80$) suggesting that mean CBCL-MS score did not change significantly in the year preceding onset compared to previous scores.

Discussion

Using prospective repeated CBCL-MS data from the TRAILS population cohort we charted the trajectories of subclinical manic states from age 11 to age 16 years. TRAILS participants at age 11 were classified according to their CBCL-MS profile to an asymptomatic, mildly symptomatic or highly symptomatic class. Our key objective was to determine whether longitudinal changes in subclinical manic states or specific symptom dimensions can differentiate TRAILS participants who convert to BD by age 19 years (converters) from those who do not (non-converters) within each class.

We found that the CBCL-MS profile at age 11 years was a significant determinant of subsequent longitudinal change between converters and non-converters. In the asymptomatic class, both converters and non-converters showed an increase in CBCL-MS total and factor scores between assessment wave 1 and 3. The mean change and the mean rate of change were greater for converters. In the mildly symptomatic class both converters and non-converters followed similar trajectories of decrease in CBCL-MS scores. In the highly symptomatic class, the trajectories of converters and non-converters diverged significantly. Non-converters showed progressive decrease in psychopathology while converters evidenced persistence (but no exacerbation) of subclinical manic symptoms.

The results from the highly symptomatic group accord with previous observations by Tijssen et al (2010) who rated manic symptoms over an average of 8 years in a representative population sample of youth, aged 14–24 years at baseline, living

around Munich, Germany.²¹ In their study, individuals having two or more manic symptoms in more than one assessment had a higher risk of conversion to syndromal BD; the odd ratio for conversion increased with the number of symptoms and the degree of persistence. However, our data suggest that those who were asymptomatic in childhood but later convert to BD show a significant increase in hypomanic symptoms. For those with mild childhood psychopathology conversion to syndromal BD was not linked to differential changes in subclinical manic states compared to those who did not. If anything, conversion seems to occur despite a pre-onset improvement in CBCL-MS scores. Clear definable persistence in symptom ratings was only seen in the highly symptomatic class where it was associated with conversion while significant symptomatic improvement was observed in non-converters.

These results seem to reconcile divergent views with regards to the early natural course of BD. Studies of children referred to psychiatric services and diagnosed with “mood dysregulation” or with atypical BD suggest that manic symptoms are present from childhood and persist as children become older.^{33, 34} These clinical populations are also enriched in risk factors for BD particularly cognitive dysfunction and parental psychiatric morbidity.^{33,34} We suggest that the converters in the highly symptomatic group conform to the pattern described above.

Patients with BD often recall having subclinical manic symptoms for many years prior to the onset of BD.⁴⁻¹¹ The description is commonly of gradually increasing psychopathology over 6-8 years.^{4,7} We propose that converters in the asymptomatic group are likely to conform to the pattern described above. The level of subclinical manic symptoms although increasing between assessment waves it still quite low and within normal variation. This may also explain the difficulty in identifying these symptoms as indicative of pathology and the delays in recognising the disorder.^{4,7}

In the mildly symptomatic group conversion occurred despite overall reduction in psychopathology over time. It is worth noting that parents of children in this class endorsed few CBCL-MS item (average of 5) with no evidence of clustering (Table 2). It is also worth noting that proportionally more cases of BD occurred in this group compared to the other two. In this respect, the pattern seen here is consistent with

other epidemiological studies that have reported increased risk for BD in adolescents that seem well-adjusted and have above average academic performance during the premorbid phase of their illness.

None of the analyses conducted suggests that BD is preceded by a distinct and definable worsening of subclinical manic symptoms that could reliably differentiate converters from non-converters.

This study has several strengths, primarily the availability of prospective data on subclinical manic states spanning the entire period of adolescence from a representative population sample of youth.³⁶ Additionally, assessment of manic symptoms was not influenced by recall or attribution and case ascertainment was not biased by help-seeking behavior, impairment or symptom severity. The prevalence of BD in this sample was consistent with that reported in other population studies. The use of the CIDI may have limited the amount of information elicited which has the potential of missing more mild syndromal presentations. As the TRAILS cohort is still going through the period of risk for syndromal conversion further cases of BD may present in the future. The CBCL-MS does not record information about episodicity considered by many a salient predictor of syndromal BD in youth.³³ We did not consider the potential contribution of depressive symptoms in any of our models. However, in this sample only 6 out of the 69 individuals that presented by BD had had a previous diagnosis of depression.

In conclusion, the findings of this study reconcile previous conflicting views regarding the early natural history of BD and suggest that the degree and pattern of childhood subclinical manic states remains a key predictor of subsequent BD.

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Table 1. Characteristics of TRAILS members and BD cases according to class membership at age 11			
	Asymptomatic Class (N=862)	Mildly Symptomatic Class (N=845)	Highly Symptomatic Class (N=199)
Total TRAILS Sample			
Sex (% Male)	39.7	54.0	67.8
CBCL-MS Scores at age 11	42.06(2.73)	53.01(4.80)	71.40(7.34)
Distractibility/Disinhibition Factor Scores at age 11	41.92(2.55)	53.23(5.15)	71.03(6.65)
Psychosis Factor Scores at age 11	45.83(4.66)	51.07(8.85)	63.70(15.78))
Disrupted Sleep Factor Scores at age 11	47.33(6.43)	51.11(10.86)	56.44(13.92)
Increased Libido Factor Scores at age 11	48.91(8.06)	49.79(7.83)	56.04(20.01)
Mean Number of symptoms	1.36(1.15)	5.76(1.89)	10.37(2.07)
Family Function	1.68(0.35)	1.82(0.33)	1.97(0.35)
IQ	101.13(14.16)	96.93(14.67)	92.02(13.63)
% Positive Parental Psychiatric Morbidity	36.9	48.5	65.8
% High SES	35.5	19.8	11.6
% Positive History of Disruptive Behavior Disorders prior to Age 11 ^a	4.19	11.03	27.19
% Positive History of any Psychiatric Diagnoses prior to Age 11 ^b	5.54	13.31	29.82
BD Cases Arising from each Class			
Number (N)	14	33	15
Age of Onset	15.57(2.06)	15.45(2.33)	15.67(2.23)
Sex (% Male)	50	57.6	46.7
CBCL-MS Scores at age 11	42.41(2.08)	54.79(5.44)	72.49(10.20)
Distractibility/Disinhibition Factor Scores at age 11	42.22(1.92)	54.41(4.56)	70.36(7.30)
Psychosis Factor Scores at age 11	47.18(4.77)	52.19(8.91)	69.38(21.39)
Disrupted Sleep Factor Scores at age 11	46.59(5.90)	53.67(13.57)	58.68(16.25)
Increased Libido Factor Scores at age 11	48.31(0.00)	50.53(12.75)	53.20(18.91)
Mean Number of symptoms	1.5(0.85)	6.36 (2.09)	10.87(3.02)
Family Function	1.77(0.28)	1.87(0.38)	1.97(0.34)
IQ	98.29(14.06)	95.18(14.24)	97.40(14.25)
% Parental Psychiatric Morbidity	35.7	51.5	66.7
% High SES	42.9	27.3	13.3
% Positive History of Disruptive Behavior Disorders prior to Age 11 ^a	14.29	27.27	40.0
% Positive History of any Psychiatric Diagnoses prior to Age 11 ^b	14.29	30.30	40.0
Continuous data are presented as mean (standard deviation); Categorical data are presented as proportions (%) within classes; ^a Includes positive history of ADHD, CD or ODD; ^b Includes positive history of MDD, GAD and disruptive behavior disorders			

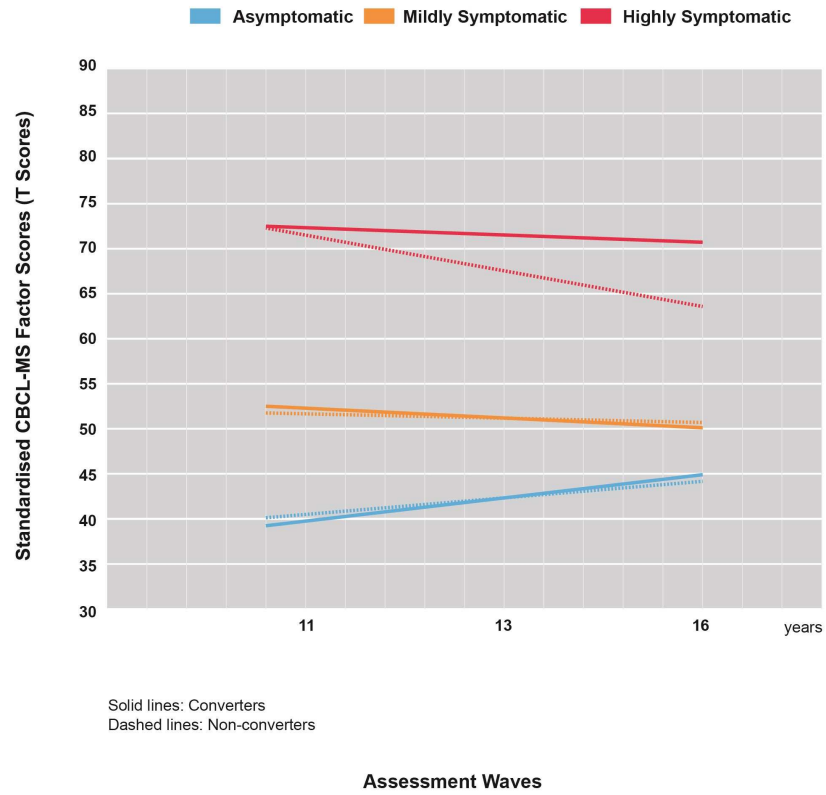
Table 2. Probability of parental endorsement of CBCL-MS items per class

CBCL-MS Items	Probability of parental endorsement		
	Asymptomatic Class	Mildly Symptomatic Class	Highly Symptomatic Class
Inattentive or easily distracted	0.01	0.10	0.61
Can't sit still, restless or hyperactive	0.00	0.10	0.55
Impulsive or acts without thinking	0.00	0.04	0.49
Unusually loud	0.00	0.01	0.42
Talks too much	0.00	0.08	0.41
Showing off or clowning	0.00	0.01	0.32
Sudden changes in mood or feelings	0.00	0.02	0.22
Teases a lot	0.00	0.01	0.15
Gets in many fights	0.00	0.00	0.08
Thinks about sex too much	0.00	0.00	0.04
Feels others are out to get him/her	0.01	0.04	0.20
Suspicious	0.00	0.01	0.11
Strange ideas	0.00	0.00	0.03
Sees things that aren't there	0.00	0.00	0.02
Hears sound or voices that aren't there	0.00	0.00	0.01
Sleeps less than most kids	0.02	0.09	0.19
Trouble sleeping	0.01	0.07	0.16
Plays with own sex parts too much	0.00	0.00	0.01
Plays with own sex parts in public	0.00	0.00	0.01

Figure 1. The factor structure of the CBCL-MS

The factor structure of the Child Behaviour Checklist – Mania Scale			
Distractibility/Disinhibition	Psychosis	Increased Libido	Disrupted Sleep
Impulsive or acts without thinking	Suspicious	Plays with own sex parts too much	Sleeps less than most kids
Can't sit still, restless or hyperactive	Has strange ideas	Plays with own sex parts in public	Trouble sleeping
Inattentive or easily distracted	Feels others are out to get him	Thinks about sex too much	
Sudden changes in mood or feelings	Hears sound or voices that aren't there		
Unusually loud	Sees things that aren't there		
Talks too much			
Teases a lot			
Showing off or clowning			
Gets in many fights			

Figure 2. CBCL-MS course by class and outcome



Supplemental Material

Representativeness of the TRAILS sample

The TRAILS cohort was identified through birth and school registers in the 5 northern municipalities of Holland. Recruitment was based on entire schools participating; 91% of all the schools in the municipalities agreed to take part. Table S1 shows that key variables regarding representativeness of the TRAILS cohort are comparable to those from the 2001 Dutch national census.

Table S1. Characteristics of TRAILS participants at enrolment compared to the 2001 national census data available online from the Centraal Bureau voor de Statistiek (www.cbs.nl)

	TRAILS	2001 Dutch Census
% Girls	50.8%	48.8% ¹
% White European	89.4%	93.2% ¹
Lower parental education ²	32.6%	30.6%
% children living with both parents ³	84.5%	84%
Median disposable household income	21780 Euros	20700 Euros

¹ The census reported on the 10-15 years age range; ² Defined as having completed up to lower half of secondary school ³ includes married and cohabiting couples

Development of the Child Behaviour Checklist-Mania Scale (full details in Papachristou et al. PloS ONE 2013)

We followed a typical content validity procedure (Grant & Davis, 1997; Lengua et al, 2001) which involves content experts who judge each item of an instrument against the definition of the domains intended to measure and score its relevance on a 4-point scale ranging from 1 (irrelevant) to 4 (highly relevant). In our study, content validity was assessed by a panel of 10 qualified child and adolescent psychiatrists (average number of years of clinical and research experience: 8; range: 4–20 years). These experts were representative of the professional settings (inpatient, outpatient, academic) within the South London and Maudsley NHS Foundation Trust. They rated the relevance of each item from the total item pool of the CBCL 6-18 on a scale of 1-4 against each of the symptom domains that correspond to operational criteria for mania of both the Diagnostic Statistical Manual for Mental Disorders (www.dsm-5.org) and the International Classification of Diseases

(www.who.int/classifications/icd). In addition, the panel considered CBCL items relating to psychotic-like experiences as childhood and adolescent. Our decision was largely based on data suggesting that psychotic symptoms are strongly associated with BD (OR=14.8; 95%CI 8.7-25.2) (van Os et al., 2000) and that psychosis prone individuals are much more likely (29% vs 5%) to develop BD (Verdoux & van Os, 2002). The content validity index (CVI) for each item was established by calculating the proportion of experts scored it as relevant (score 3) or highly relevant (score 4) for any of the domains. A minimum item CVI of 0.80 (Grant & Davis, 1997) was required for inclusion in the second stage where final item inclusion to the CBCL-MS was based on unanimous agreement. Following consensus meetings, 19 items were selected for inclusion in the CBCL- Mania Scale (CBCL-MS) (Supplemental Table S2). The scoring of the CBCL-MS at each assessment age was based on summing the scores of each of the 19 individual items. Scores were then standardized (T scores) following the scoring procedure recommended by Achenbach and Rescorla (2001) using the TRAILS data as the standardization sample. Standardization of the CBCL scores for the CBCL-MS, as well as for other CBCL-based syndrome scales, was performed separately for each wave.

Table S2. Child Behavior Checklist-Mania Scale items and corresponding core and extended criteria for Mania

CBCL Items	DSM-IV criteria for Mania
Core Symptoms	
37. Gets in many fights	A distinct period of abnormally and persistently elevated, expansive or irritable mood
87. Sudden changes in mood or feelings	
96. Thinks about sex too much	Inflated self-esteem or grandiosity
74. Showing off or clowning	
94. Teases a lot	Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
76. Sleeps less than most kids	
100. Trouble sleeping	More talkative than usual or pressure to keep talking
93. Talks too much	
104. Unusually loud	Flight of ideas or subjective experience that thoughts are racing
78. Inattentive or easily distracted	Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
10. Can't sit still, restless or hyperactive	Increase in goal-directed activity (at work, at school, or sexually) or psychomotor agitation
60. Plays with own sex parts too much	
41. Impulsive or acts without thinking	Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
59. Plays with own sex parts in public	
Extended Symptoms	
34. Feels others are out to get him/her	Delusions
85. Strange ideas	
89. Suspicious	Hallucinations
40. Hears sound or voices that aren't there	
70. Sees things that aren't there	
Items numbered as in the Child Behaviour Checklist (6/18)	

Psychometric Properties and Discriminative value of the Child Behaviour Checklist-Mania Scale

Reliability analysis demonstrated high internal consistency for the 19 items of the CBCL-MS at all assessment ages (Cronbach's $\alpha \geq .80$; total item correlation > 0.37).

Based on Receiver Operator Curve (ROC) analysis on the CBCL-MS data the area under the curve (AUC) was 0.64 ($p < 0.01$) which represents a satisfactory performance for a general population sample. A forward stepwise logistic regression model showed that the CBCL-MS had significantly increased ability to predict BD compared to the CBCL-Pediatric Bipolar Disorder scale (Wald $\chi^2 = 12.69$, $p < .001$) and the CBCL-Externalizing Scale (Wald $\chi^2 = 3.47$, $p = .05$).

Reliability analyses demonstrated high internal consistency for the 19 items of the CBCL-MS at all assessment ages (Cronbach's $\alpha \geq 0.80$; item total correlation > 0.37). PCA analyses of the CBCL-MS data at ages 11, 13 and 16 years resulted in an almost identical factor structure and explained 48.18%, 46.06% and 44.94% of the variance of the items respectively. The four factors corresponded to: (1) distractibility/ disinhibition (2) psychotic symptoms (3) increased libido (4) disrupted sleep. Items' loading for the four factors are shown in Tables S1-S3. Parallel analyses and Kaiser's criterion both supported the retention of four factors. The scree plot of the extracted eigenvalues from the parallel analysis at age 16 is given in Figure S1. Fit indices of Confirmatory Factor Analyses (CFA) established good fit of the data [Root Mean Square Error of Approximation (RMSEA) values were 0.04, 0.04 and 0.05, and Confirmatory Fit index (CFI) values were 0.97, 0.96 and 0.92 for the three assessment points respectively].

Table S3. Items, factors and item loadings of the CBCL-MS at age 16

Manic Items	Distractibility/ Disinhibition	Psychotic Symptoms	Disrupted Sleep	Increased Libido
41. Impulsive or acts without thinking	.711	.109	.043	.025
10. Can't sit still, restless or hyperactive	.680	.053	.081	.108
78. Inattentive or easily distracted	.676	.002	.117	.047
104. Unusually loud	.672	.177	.038	.073
74. Showing off or clowning	.637	.092	.018	.070
93. Talks too much	.623	.007	.103	-.047
94. Teases a lot	.423	.390	-.145	.159
87. Sudden changes in mood or feelings	.411	.299	.237	-.093
96. Thinks about sex too much	.407	-.026	.201	.001
85. Strange ideas	.028	.662	.301	-.101
37. Gets in many fights	.290	.534	-.131	.225
70. Sees things that aren't there	-.027	.464	.326	-.054
40. Hears sound or voices that aren't there	-.074	.457	-.054	.137
89. Suspicious	.406	.448	.150	-.169
34. Feels others are out to get him/her	.384	.436	.055	-.108
100. Trouble sleeping	.162	.127	.796	.030
76. Sleep/s less than most kids	.209	.038	.769	.097
59. Plays with own sex parts in public	.029	.109	.055	.793
60. Plays with own sex parts too much	.086	-.043	.038	.749

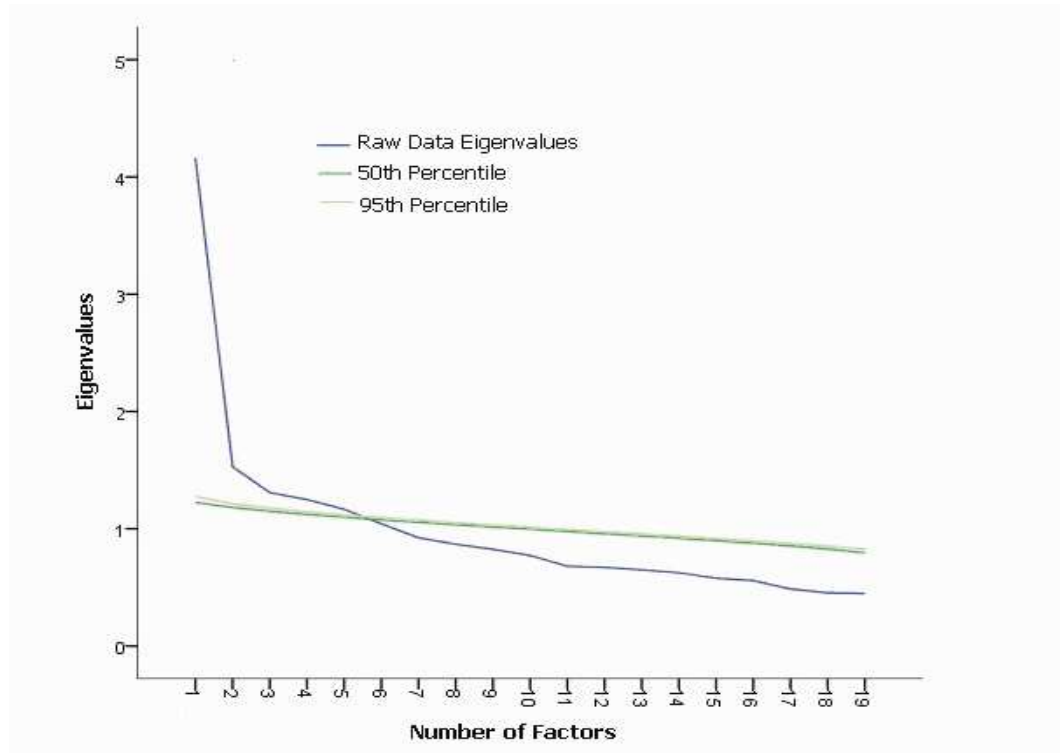
Table S4. Items, factors and item loadings of the CBCL-MS at age 13

Manic Items	Distractibility/ Disinhibition	Psychotic Symptoms	Increased Libido	Disrupted Sleep
41. Impulsive or acts without thinking	.704	.055	.014	.061
104. Unusually loud	.696	-.022	.024	.108
10. Can't sit still, restless or hyperactive	.695	-.041	.060	.052
78. Inattentive or easily distracted	.680	.068	.050	.080
74. Showing off or clowning	.671	.126	-.021	-.029
93. Talks too much	.597	-.033	-.035	.158
94. Teases a lot	.561	.213	.120	-.053
87. Sudden changes in mood or feelings	.489	.169	-.013	.226
89. Suspicious	.406	.394	-.087	.152
37. Gets in many fights	.399	.273	.119	-.122
96. Thinks about sex too much	.313	.176	.272	-.048
70. Sees things that aren't there	-.003	.789	-.063	.025
40. Hears sound or voices that aren't there	-.036	.664	.140	.056
34. Feels others are out to get him/her	.116	.497	.050	.095
85. Strange ideas	.347	.371	-.023	.107
60. Plays with own sex parts too much	-.017	.076	.842	.045
59. Plays with own sex parts in public	.054	-.029	.825	.015
76. Sleeps less than most kids	.097	.117	.014	.827
100. Trouble sleeping	.125	.115	.031	.803

Table S5. Items, factors and item loadings of the CBCL-MS at age 11

Manic Items	Distractibility/ Disinhibition	Psychotic Symptoms	Disrupted Sleep	Increased Libido
104. Unusually loud	.750	.128	.049	.055
74. Showing off or clowning	.706	.140	.046	.048
10. Can't sit still, restless or hyperactive	.681	.017	.077	.055
78. Inattentive or easily distracted	.678	.076	.064	.049
41. Impulsive or acts without thinking	.676	.138	.034	.098
94. Teases a lot	.628	.078	.041	.031
93. Talks too much	.585	.047	.072	.075
87. Sudden changes in mood or feelings	.532	.306	.094	-.086
37. Gets in many fights	.524	.037	.001	.179
70. Sees things that aren't there	.027	.706	.073	.053
40. Hears sound or voices that aren't there	-.071	.685	.018	.182
85. Strange ideas	.185	.539	.070	.086
89. Suspicious	.329	.483	.100	-.039
34. Feels others are out to get him/her	.392	.470	.031	-.108
76. Sleeps less than most kids	.138	.067	.857	.030
100. Trouble sleeping	.065	.166	.843	.009
60. Plays with own sex parts too much	.082	.041	-.034	.825
59. Plays with own sex parts in public	.003	.214	-.050	.703
96. Thinks about sex too much	.267	-.050	.174	.476

Figure S1. Scree Plot of parallel analysis at age 16



Characteristics of patients with Bipolar Disorder per class

Table S6. Characteristics of cases with syndromal BD by age 19 according to class membership at age 11

	BD cases arising from the Asymptomatic Class (N=14)	BD cases arising from the Mildly Symptomatic Class (N=33)	BD cases arising from the Highly Symptomatic Class (N=15)
% of all cases with Bipolar Disorder in the TRAILS sample	16.2	38.37	17.4
Male: Female ^a	1.0:1.0	1.0:0.7	1.0:1.1
% High SES ^b	35.3	52.9	11.8
IQ ^c	98.29 (14.06)	95.18 (12.30)	97.40 (14.25)
% Parental Psychiatric Morbidity ^d	15.6	53.1	31.2
Age of Onset of BD (years) ^e	15.57 (2.06)	15.45 (2.33)	15.67 (2.22)
% Previously Diagnosed with Disruptive Behaviour Disorders ^f	11.8	52.9	35.3
Continuous data are presented as mean (standard deviation); Categorical data are presented as proportions (%) across classes; ^a $\chi^2=0.57$, $p=0.75$; ^b $\chi^2=3.84$, $p=0.43$ ^c $F_{(2,59)}=0.33$, $p=0.72$; ^d $\chi^2=2.78$, $p=0.25$; ^e $F_{(2,59)}=0.05$, $p=0.95$; ^f $\chi^2=2.40$, $p=0.30$			

7 Discussion

7.1 Introduction

This chapter will commence by presenting a summary of the main findings of the thesis. Next, the main strengths and limitations of the studies comprising Chapters 4 to 6 (**Chapter 4. Child Behavior Checklist- Mania Scale (CBCL-MS): Development and validation of a population-based scale for bipolar disorder; Chapter 5. Alarm Symptoms in the Early Diagnosis of Bipolar Disorder: A Population Based Cohort Study; and Chapter 6. Trajectories to Bipolar Disorder from Childhood to Adulthood**) will be highlighted, followed by an integration of the results. The chapter will conclude by outlining future directions and suggesting priorities of research in this field.

7.2 Summary of the main findings

Numerous implications of the studies comprising this thesis have been discussed in the previous chapters; overall, there are six main findings. Firstly, I have now developed a new scale, termed CBCL-MS, which measures manic symptomatology using 19 items of the widely used CBCL 6-18 (Achenbach & Rescorla, 2001). This scale improves already existing scoring algorithms using the CBCL to measure manic symptomatology (Biederman et al., 1995; Faraone et al., 2005; Kim et al., 2012) and therefore it posits a great step forward in the attempts to develop better assessment tools for common mental disorders. Most importantly it is based on items of the CBCL which is a widely used instrument that has been translated in over 90 languages and has cross-cultural generalisability (De Groot et al., 1994). The structural model of the CBCL-MS consisted of four factors. These factors correspond to dimensions of distractibility/disinhibition, psychosis, increased libido and disrupted sleep. The factor structure of the CBCL-MS showed remarkable temporal stability between the ages of 11 to 16. It also presented with good internal consistency as well as discriminatory ability in distinguishing bipolar from non-bipolar cases.

Secondly, I have successfully identified a group of children aged 11 years that are at high risk to develop BD one to eight years after the initial assessment using the CBCL-MS. Specifically, using a Latent Class Analysis to empirically characterize children based on parental endorsement of subclinical manic manifestations, a 'mildly symptomatic' and a 'highly symptomatic' class of children were extracted who were 2.7 and 7.1 times, respectively, more likely to develop BD by age 19 years in comparison to the reference 'asymptomatic' class. Children in the 'highly symptomatic' class were also characterized by a confluence of sociocognitive and familial risk factors, including lower IQ, worse family functioning, low socioeconomic status and higher rates of parental psychiatric morbidity.

Thirdly, we introduced the concept of 'alarm symptoms' for BD by drawing example from research in the early detection of cancer which can be used to formulate prevention strategies pending more detailed biological validation (Post et al., 2013). These included clustering of CBCL-MS items of hyperactivity, impulsivity, clowning, reduced sleep, mood lability and increased and loud speech that were endorsed with a probability of ≥ 0.3 resulting in standardized CBCL-MS total score ≥ 70 . The positive and negative predictive value of the "alarm symptoms" identified was 13.2% and 96.3% respectively.

Fourthly, class membership was a significant predictor of BD but not of major depressive disorder, general anxiety disorder or substance abuse. This specificity of prediction represents an additional step forward in the study of mental disorders as most familial and non-familial risk factors have been shown to predict multiple adverse outcomes. Such a pluripotent effect of risk factors has been shown, for example, for family history of schizophrenia which increases the probability of multiple other adverse mental health outcomes (Dean et al., 2010).

Moreover, I have shown that manic symptoms in adolescent populations are common, consistent with previous reports (Shankman et al., 2009; Tijssen et al., 2010a).

Finally, by charting the trajectories of manic symptomatology spanning from late childhood to late adolescence I have demonstrated that youths who do not convert to BD show a decrease in the numbers of psychopathology during adolescence while those who converts evidence persistence but no exacerbation of subclinical manic symptoms.

7.3 Strengths and Limitations

7.3.1 Strengths

The studies presented as part of this thesis present with multiple strengths and advantages. Firstly, I advocated a life course approach to the study of BD which, as described in Chapter 1, presents with several advantages over cross-sectional research designs. Additionally, the analytical procedures followed were chosen carefully and I did not solely rely on traditional univariate linear analyses that do not reflect the full complexity of the events by relying on rather strict assumptions of error free variables (Bollen and Curran, 2006). The longitudinal collection of data by TRAILS also adds value to the study of the course of manic symptoms over early life stages. Traditionally, longitudinal study designs have been shown to provide more efficient estimators than cross-sectional designs with same number and pattern of observations; in addition, they also allow the identification of aging effects (changes over time within individuals) from cohort effects (differences between subjects at baseline) and have therefore the potential to provide information about individual change (Hedeker et al., 2004).

Moreover, the sample of TRAILS is a large representative community sample that provided the ideal ground for generating and testing aetiological models for mental health. Gender and sociodemographic variables were adequately represented in the sample and the prevalence rate of 5.4% for BD coincides with the one reported in a recent epidemiological study of US adolescents (Kessler et al., 2009) providing additional support for the representativeness of the sample. The sample size was also large enough to result in an adequately powered study.

Moreover, this study provides unique insight in the study of BD as it examined the longitudinal course of subclinical manic symptoms, while incorporating risk factors in the analytical process to account for the additional variance explained by these variables. These variables included socioeconomic status, cognitive abilities, family history of psychopathology and family functioning which have been consistently shown to be associated with increased risk and/or worse prognosis for patients with BD (Du Rocher Schudlich et al., 2008; Koenen et al., 2009; Kumar and Frangou 2010; Bauer et al. 2011). These variables were adequately measured with instruments, which have been shown to have excellent psychometric properties (see Chapter 3).

7.3.2 Limitations

The results of this thesis and their implications should be viewed in light of its limitations. Firstly, the study period does not cover the full risk period for BD and it is possible that further cases may present in the future. In fact, while BD commonly begins in adolescence with a modal age of onset between 16 and 20 years (Roy-Byrne et al., 2007; Mesman et al., 2013), almost half of the patients with Bipolar-I have reported an age of onset after the age of 25 years in the world mental health survey initiative (Merikangas et al., 2011). Therefore, our results are limited to what would be considered to be early onset BD in the available literature.

Inherent in research in social sciences are also limitations of the instruments used including measurement error and assessment biases. For example, despite its widespread use, the CIDI is limited by its structured format and its administration by lay interviewers who may not probe or interpret further participant responses. In addition, Kessler et al. (2006) have highlighted that the positive predictive value of the CIDI-based screening scales is likely to vary across populations as a function of the prevalence of the targeted disorder and therefore the estimates of BD found in TRAILS cannot be assumed to hold in all other settings.

Other sources of error could have related to the informant. For the studies of this thesis I used parental reports of symptoms captured with items of the CBCL 6-18 to measure subclinical manic symptomatology. Research suggests that no single rater can provide a complete picture of the child's behavior and, more importantly, that parents commonly assess different aspects of the child's behavior (Bartels et al., 2003). In order to tackle this limitation it is important for future studies to validate the findings of my work using data from multiple sources such as teacher ratings or self-reports. For this purpose, other assessment tools included in the Achenbach System of Empirically Based Assessment (ASEBA) battery of tests, e.g. the Teacher Report Form (TRF) or the Youth Self-Report (YSR) can be used (Achenbach, 1991).

Subject loss at follow-up assessments is also a common form of selection bias in longitudinal study designs (Kristman et al., 2004). Acceptable follow-up rates have been recommended to be from 50% (Babbie, 1990) to 80% (Altman, 2000). However, at 84.3% almost 10 years after the baseline assessment, attrition rate has been kept very low in TRAILS. In addition, missing data were treated appropriately in order to correct for bias and minimize error (Chapter 3.6).

7.4 Integration of Findings

The findings of the studies presented in this thesis build on the currently available body of literature on the measurement and course of BD and expand them in new directions. The development of the CBCL-MS is a significant step forward in the attempts to develop valid and reliable and assessment tools for psychiatric symptomatology. Particularly for BD, there are numerous scales available that have been shown to have moderate to good predictive value and discriminant ability with manic symptomatology (Youngstrom et al., 2004). These include the Parent Young Mania Rating Scale (P-YMRS; Gracious et al., 2002;), the Parent General Behavior Inventory (P-GBI) (Youngstrom et al., 2001), the Adolescent General Behavior Inventory (A-GBI) (Danielson et al., 2003), the Youth Self Report (YSR) (Achenbach et al., 1991), the Teacher Report Form (TRF) (Achenbach et al., 1991), the Childhood Mania Rating Scale (CMRS) (Pavuluri et al., 2006), the Mood Disorder Questionnaire-Adolescent Version (MDQ-A) (Wagner et al., 2006) and others.

The psychometric properties of the newly developed CBCL-MS compare to the ones achieved by widely used instruments, e.g. the MDQ, in large community samples (Hirschfeld et al., 2003). Most importantly, the CBCL-MS was developed using items of the widely used CBCL 6-18 (Achenbach, 1991) and constitutes a better scoring algorithm for BD than the already existing ones, i.e. the CBCL-Pediatric Bipolar Disorder (Faraone et al., 2005) and the Externalising Scale of the CBCL (Diler et al., 2009).

Noticeably, the CBCL-MS could not differentiate participants with BD from those with ADHD confirming that the relationship between these two disorders is complex. More evidence on the suggested overlap in the symptoms of the two disorders particularly with regards to increased activity, talkativeness and mood dysregulation (WHO, 1992; APA, 1994) stemmed from the analyses in Chapter 5. A large proportion of children in the highly symptomatic class had childhood diagnoses of disruptive behavior disorders, particularly ADHD. It would therefore appear that behavioral measures and risk factors, even when considered together, do not allow sufficient separation between ADHD and childhood antecedents of BD. This suggests that either the two disorders have overlapping pathophysiology or that measures with greater biological specificity are needed to differentiate between the two (Skirrow et al., 2012).

Moreover, membership to the highly symptomatic risk class (Chapter 5) was not associated with higher risk for future major depressive disorder, general anxiety disorder or substance abuse; yet, 62 individuals (30%) of this class had such non-BD diagnoses by age 19. In combination with findings suggesting that subclinical BD symptoms are associated with elevated impairment, comorbidity, and suicide attempts (Lewinsohn et al., 2003), this type of classification might prove very useful from a public health perspective.

In addition, the frequent endorsement of subclinical manic symptoms, particularly for participants in the highly symptomatic class, are in line with the body of research

suggesting that subclinical manic symptomatology is common in adolescence (Tijssen et al., 2010a) and highlights the possible advantages of expanding the concept of syndromal BD to include subthreshold manic-like pathology and BD-NOS in children and adolescents (Angst et al., 2003; Geller et al. 2007; Stringaris et al. 2010). Specifically, Stringaris et al. (2010) demonstrated that by relaxing the duration criterion the prevalence of youths with BD-NOS was 10-times higher than the prevalence of actual BD. Youths with BD-NOS demonstrated very poor overall social functioning emphasizing further the need to follow-up the children of my study belonging to the highly symptomatic class and assess their functional and psychiatric outcome over a longer period of time.

Finally, with regards to the subclinical manic symptoms charted in Chapter 6, our findings suggest that subclinical manic symptomatology in asymptomatic or mildly symptomatic children at age 11 follow similar longitudinal trajectories for those who convert to BD and those who do not. In contrast, converters in the highly symptomatic class showed persistence of subclinical symptomatology prior to BD onset while non-converters evidenced a rapid decrease. These findings build on the evidence reviewed in Chapter 6 which suggests that the odds for conversion increase with the degree of persistence of manic symptoms (Tijssen et al., 2010b). Specifically, this pattern was confirmed only for children in the highly symptomatic class who subsequently converted to BD, emphasizing the importance of more person centred-approaches in the study of longitudinal change and rate of change of psychopathology and therefore in the identification of future strategies for early identification and prevention.

7.5 Future Directions

The studies presented as part of this thesis build on the existing literature and open up interesting new avenues in the study of BD. In this section I will highlight the main research priorities as exemplified by the results presented.

Firstly, the CBCL-MS should be tested in other epidemiological samples to establish its usefulness as a screening instrument. In an exploratory manner the scale could be

tested in clinical samples to examine whether it can also serve as a diagnostic instrument complementary to other established clinical diagnostic instruments. Convergence with valid and reliable instruments as well as inter-rater agreement rates would be essential in this process (Kline, 1988). The discriminative abilities of the scale have the potential to improve greatly as a result of the increased base rate which is directly tied to the positive and negative predictive values of a screening instrument (Glaros & Kline, 1988).

Future studies should also follow and assess children in the highly symptomatic class to examine whether the conversion rates, and therefore the positive predictive value, increase due to additional cases presenting with BD in the next years. Since the period covered by the assessments in TRAILS do not cover the full risk period for BD it is possible that youths in the highly symptomatic class haven't converted to BD as yet.

Moreover, it would be pertinent to identify additional unique characteristics of children in the highly symptomatic class who convert to clinically meaningful BD. These characteristics could extend beyond the sociodemographic, familial and cognitive characteristics included in the analyses of my studies to include neuroimaging and/or genetic data. Recent studies have identified genetic risk factors (Kakiuchi et al., 2003; Schumacher et al., 2004; Moskvina et al., 2008) as well as structural and functional brain abnormalities (Strakowski et al., 2004) that are associated with an increased risk of BD. This type of cross-disciplinary research combining epidemiological psychiatric research with research in genetic markers and neuroimaging can expand my results by identifying additional risk markers or resilience factors for BD and therefore explain more variability in the mechanisms leading to conversion from risk to full syndromal status.

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Review article

Expanding conceptual frameworks: Life course risk modelling for mental disorders

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ABSTRACT

Psychiatric epidemiology has made significant contributions to the identification of risk factors for mental disorders. Available evidence underscores the complexity of the interactions between risk and disease and highlights conceptual and methodological challenges particularly in examining risk and disease relations beyond the level of simple associations. We propose that a life course approach in the study of risk factors for mental disorders, combined with fast developing analytical statistical tools, is the most promising avenue towards shifting the focus of the field from associations to generating and testing aetiological hypotheses. This review presents the basic tenants of life course risk modelling, highlighting key examples in the available literature that demonstrate the potential of this approach to advance our understanding of the trajectories from risk to disease and discusses priorities for future research.

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Contents

1. Introduction	140
2. Life course approaches in epidemiology	141
2.1. Critical periods	141
2.2. Accumulation of risk	141
3. Life course approaches within the psychiatric epidemiological research	141
3.1. Critical periods	142
3.2. Accumulation of risk	142
3.3. Traditional multivariate analyses vs. statistical modelling techniques	143
4. Directions for future research	143
References	144

1. Introduction

Psychiatric epidemiology and especially analytical epidemiological studies have made great advances in identifying multiple risk factors for mental disorders, particularly for schizophrenia, mood disorders and anxiety disorders. Across diagnostic categories key risk factors include low socioeconomic status (SES) (Danese et al., 2009), familial psychopathology (Lichtenstein et al., 2009), stressful life events (SLEs) (Kendler et al., 1999), low IQ (Koenen et al., 2009), family dysfunction (Bouma et al., 2008) and cannabis use (Degenhardt et al., 2007). Although informative,

these reports are commonly limited to simple associations between a risk exposure and a later adverse mental health outcome while the timing and exact mechanism of this transition remain largely unstudied. Here we advocate a life course approach in the study of risk factors for mental disorders as this has the potential to advance our understanding of the trajectories from risk to disease.

Within the current cohort designs, life course formulations have the potential to shed light on the mechanisms as well as the timing of exposures underlying the development of psychopathology, especially when combined with the appropriate analytical statistical tools. The objectives of this article are threefold: (a) to complement recent reviews on early risk factors and genetic variants for common mental disorders, e.g. schizophrenia (Brown and Derkits, 2009), by highlighting the additional value of the life course approach; (b) to present the basic concepts of life course

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risk modelling; and (c) to highlight key examples for its usefulness for psychiatry and public health. The examples presented provide evidence on how the life course approach can serve as the starting point in addressing questions about mechanisms mediating between risk and disease outcome on a more fundamental level. Finally, we make specific suggestions as to how life course modelling can be more fully integrated into psychiatric epidemiological research. Such information is crucial in moving the field from an associative focus to generating and testing aetiological hypotheses.

2. Life course approaches in epidemiology

The life course approach was mostly developed within the field of cardiovascular medicine from which we draw key examples to illustrate its two basic tenants, namely critical periods and accumulated risk (Lynch and Smith, 2005).

2.1. Critical periods

Life course models recognise that the timing of exposure plays an important role in determining the risk for disease. In this context life course models focus on critical or sensitive periods. The critical period model assumes that there are stages in human development during which the influence of external agents may have crucial effects that cannot be altered by subsequent events and precipitate disease in later life. Conversely, the influence of the same agents during any other developmental stage will be minimal or absent. Implicit in the critical period model is the notion that the influence of external agents, when it occurs during this particular stage, alters the function or structure of biological tissues or systems through processes of “biological programming” so that the effect of the exposure becomes “embodied” (Kuh et al., 2003). In contrast, sensitive periods are stages in development when the influence of external agents may have the strongest effect on disease risk that could be however modified by subsequent experiences or exposures (Kuh et al., 2003). At this particular junction, the distinction between critical and sensitive periods is often blurred as the basic biological effects of exposures that could result in altered “biological programming” which are poorly understood. For simplicity and parsimony we will refer to all models focusing on the timing of exposures as critical period models.

The best evidence for the critical period concept derives from the foetal origin hypothesis in cardiovascular medicine. It proposes that adversity very early in pregnancy, and especially poor maternal nutrition, leads to impaired growth and biological programming of the foetus, thus increasing the risk of cardiovascular disease later in life (Barker, 1995; Barker and Clark, 1997; Barker and Osmond, 1986; Eriksson et al., 2001; Painter et al., 2006). The incidence of Coronary Artery Disease (CAD) is increased following exposure to famine in the first trimester of gestation but not if exposure to famine occurs in mid- or late-gestation (Painter et al., 2006).

2.2. Accumulation of risk

The accumulation of risk model suggests that exposures or insults act in a cumulative fashion to gradually increase the risk of disease or mortality. This hypothesis postulates that cumulative differential life time exposure is the main explanation for observed individual differences in disease risk (Kuh et al., 2003). Numerous studies have examined the risk accumulation hypothesis in relation to medical outcomes, health inequalities and social, physical and cognitive functioning (Power et al., 1996; Lynch et al., 1997; Smith et al., 1997; Hart et al., 1998; Power et al., 1999; Holland et al., 2000;

Wamala et al., 2001). There are two main variations to the risk accumulation hypothesis relating to whether there is prolonged exposure to a single risk factor or an interaction between multiple factors either in an additive (risk clustering) or in a sequential fashion (chains of risk) (Kuh et al., 2003).

A typical example for the prolonged exposure model was provided by Smith et al. (1997). They employed a prospective observational study design with a 21 year follow-up focusing on mortality. They examined the risk of lower SES at three time points, in childhood based on father's occupation and in early and late adulthood respectively based on own first and more established occupation. They found a cumulative effect of lower SES acting over the lifetime; people who reported belonging to the low SES group at a single measurement point had a relative death rate of 1.29 (95% CI 1.08–1.56) which increased further to 1.71 (95% CI 1.46–2.01) for those reporting belonging to the low SES group at all three measurement points. Similarly, Wamala et al. (2001) report that, in women, early and late socioeconomic advantage are respectively associated with a 2.48 (95% CI 0.90–6.83) and a 3.22 (95% CI 1.02–10.53) increase in the risk for Coronary Heart Disease (CHD). However, women with both early and late exposure had an even greater risk of 4.22 (95% CI 1.4–12.1).

We now focus on how risk factors may interact to increase risk. Different risk factors may cluster together and may act cumulatively to increase risk. For example, Luchsinger et al. (2005) demonstrated by following 1138 individuals for 5.5 years that diabetes, hypertension, heart disease, and smoking were all associated with a higher risk of Alzheimer's disease. In a subsample of people with high risk for Alzheimer's disease ($N=246$) the risk conferred by the risk factors individually ranged from 1.4 to 3.6 (adjusted for age and gender). The hazards ratios of the interactions between these factors varied greatly and were highest for the interaction of diabetes and smoking which reached 13.7 (95% CI 1.8–101.7).

Alternatively, risk factors may be linked forming chains of risk or insults whereby each exposure may lead to further adverse exposures or experiences. Each link in the chain may have an independent effect on disease risk or else disease onset may be predicated only by the final link (trigger effect; Kuh et al., 2003). Dong et al. (2004) provide a detailed example of this model in relationship to ischaemic heart disease. They mapped the pathway from childhood adversities (including abuse, neglect and household dysfunction) to increased reactivity to stress leading to increased risk for negative affective states. Negative affective states (depression or anger) are now known to cause haemodynamic, haemostatic, immunologic and other endocrine changes leading to alterations in the platelet function and increased risk of coronary ischaemia.

3. Life course approaches within the psychiatric epidemiological research

Within psychiatric epidemiology, cohort designs have the greatest potential to shed light on causal mechanisms by which exposure to risk can lead to the development of mental disorders. They provide a framework for overcoming recall biases and allow the consideration of exposures and outcomes in a temporal context. Moreover, they provide data amenable to life course analyses and are therefore the ideal ground for generating and testing aetiological models for mental health. The most prominent birth cohorts include the Dunedin Multidisciplinary Health and Development Study (DMHDS) (Silva, 1990), the British 1946 Birth Cohort (BBC) (Wadsworth, 1987), the National Child Development Study (NCDS) (Power and Elliott, 2006), the 1970 British Cohort Study (BCS) (Ferry et al., 2003), the Northern Finland 1966

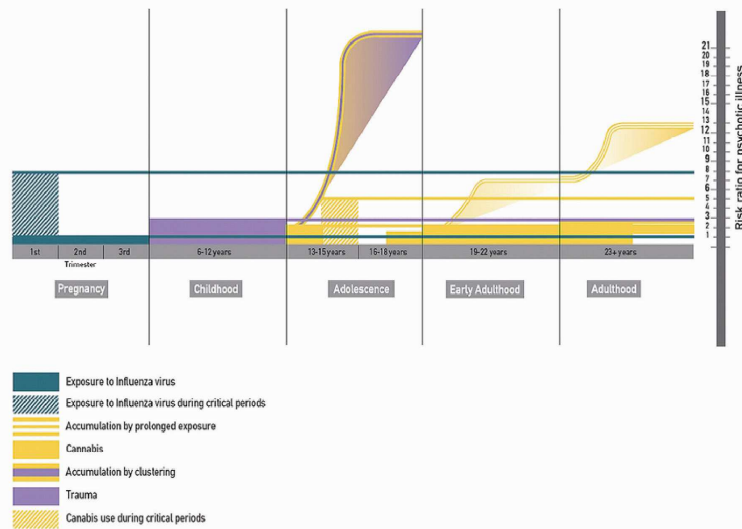


Fig. 1. Critical periods of risk exposure and cumulative interactions of risk factors for psychotic illness: an illustrative example of the most prominent findings.

Birth Cohort (NFBC) (Rantakallio, 1988), the Child Health and Development Study (CHDS) (Van den Berg et al., 1988) and the Christchurch Health and Development Study (ChHDS) (Fergusson and Horwood, 2001). For these studies, 1000–20,000 individuals from well defined-geographical areas were assessed from pregnancy or birth and were followed-up at regular intervals with low to moderate attrition rates. Follow-up periods have been of sufficient length so as to capture sufficient cases of schizophrenia, depression or anxiety disorders. Findings stemming from birth cohorts have substantially contributed to the field of translational epidemiologic research, a term used to describe the application of findings into innovative primary and secondary interventions and therefore into new clinical practices and public health policies (Weissman et al., 2011). Fig. 1 summarises some of the evidence identified and illustrates the notions of critical periods and accumulation of risk while assuming that the risk conferred by genetic factors is constant.

3.1. Critical periods

Most of psychiatric epidemiology has focused on the notion of critical periods with main emphasis on the foetal and adolescent periods. Similarly to medical disorders, prenatal exposure to famine has been also shown to play a significant role for the development of mental disorders. Brown et al. (2000) provide an early example of significant associations between exposures to prenatal famine during the second and third trimester and major affective disorder in adulthood. Exposures to the rubella (Brown et al., 2001) and the influenza virus (Brown et al., 2004) during pregnancy are strongly associated with adult schizophrenia; specifically, the risk for psychotic illness in adulthood may increase 7-fold, (95% CI 0.7–75.3) following exposure to the influenza virus during the first trimester of gestation. In contrast, exposure to the same virus during the second or third trimester confers smaller risk [2nd trimester: 1.1 (95% CI 0.3–3.9); 3rd trimester: 1.1 (95% CI 0.5–2.6)].

Adolescence is also commonly considered a critical period because of documented evidence for brain maturation processes

(Whitford et al., 2007) and hormonal changes (Sisk and Zehr, 2005). Cannabis use during adolescence is a frequently studied risk factor for the development of psychosis (Fig. 1). Cannabis use at age 14–15 years appears to increase the risk of psychosis in adulthood by 4.50 (95% CI 1.11 to 18.21) while the risk for users at age 18 is substantially lower (1.65; 95% CI 0.65 to 4.18) (Arseneault et al., 2002) and is similar to that observed following cannabis use in early adulthood [1.68 (95% CI 0.37–7.51)] (Grech et al., 2005).

3.2. Accumulation of risk

Relatively fewer studies have examined the accumulation of risk models with most recent examples focusing on the role of cannabis. In addition to influencing risk during critical periods, the effect of cannabis on the risk for psychosis increases further with greater and more prolonged duration of exposure (Grech et al., 2005; Semple et al., 2005) (as illustrated in Fig. 1). Furthermore, cannabis appears to act synergistically with other risk factors to increase and maintain the risk for psychosis (Counnard et al., 2007; Houston et al., 2008; Harley et al., 2010). A typical example is provided by Harley et al. (2010), who examined the interactions between childhood trauma and cannabis use with respect to the development of psychotic symptoms (Fig. 1). In their study each risk factor independently increased the risk of psychotic symptoms. The individual risk conferred was 2.6 (95% CI 0.25–14.6) for childhood trauma and 1.9 (95% CI 0.04–16.5) for cannabis use. However, the interaction of childhood trauma and cannabis use increased the likelihood of psychotic symptoms by tenfold to 20.9 (95% CI 2.3–173.5).

In terms of chains of risk research in depression has yielded the most consistent findings to date. A common cascade of exposures leading to depression begins with maternal depression which increases the risk of family adversity (Murray et al., 1996) leading to increased reactivity to stress reflected in Hypothalamic–Pituitary Adrenal (HPA) axis dysregulation (Halligan et al., 2007). Increased stress reactivity increases the risk of negative affect during adverse life exposures and further disrupts the HPA axis. This has been

associated with reduced hippocampal volume and prefrontal cortical activation which increase the risk of clinical depression (Palazidou, 2012).

Accumulation of risk and critical periods are not two mutually exclusive models. Shanahan and Hofer (2010) have recently described how such life course models could explain the interaction between genetic and social risk factors of disease. They posit that exposure to certain social risk factors during critical or sensitive periods may not only impact on biological structure or functions but may greatly influence subsequent social experiences forming a “chain of insults” and resulting in cumulative disadvantage.

The studies illustrate the potential of life course approach in disentangling the complex architecture of risk for psychiatric disorders and in providing a deeper understanding of how different life course models might complement each other. These theoretical models when paired with fast developing statistical techniques present new opportunities for the investigation of the mechanisms of conversion to psychopathology.

3.3. *Traditional multivariate analyses vs. statistical modelling techniques*

The most common modelling approaches in psychiatric epidemiology have examined associations using logistic regression or proportional hazard models. Yet, these models are limited when employing a life time approach for two main reasons; first, they cannot estimate separate regression lines for each individual (i.e. they neglect important information on inter-individual variability) and second they rely on the assumption that the intercept and rate of change (slope) of additional explanatory variables are error free (Bollen and Curran, 2006).

These limitations can now be tackled by utilising different analytical tools that broadly fall under category of Structural Equation Modelling (SEM). These include but not restricted to Latent Growth Models (LGMs), Multivariate LGMs with or without Time In-varying Covariates (TICs) and Time Varying Covariates (TVCs), Autoregressive Latent Trajectory models (ALTs) (McArdle and Hamagami, 1992; Curran and Hussong, 2003; Bollen and Curran, 2004; Ludtke et al., 2008; MacKinnon, 2008; Rabe-Hesketh and Skrondal, 2008; Chavance et al., 2010). The advantage of these models is that they can identify the unique change in the variance of the slope and rate of growth of variables within and across individuals. This type of information would address questions concerning critical periods of exposure and accumulation of risk more precisely. Specifically, these models allow for (a) detecting patterns of non-linear change, e.g. quadratic or cubic functions (LGMs); (b) incorporating repeated measures of a covariate as a direct predictor of the repeated measures of a dependent variable in the presence of the growth process of that dependent variable (Multivariate LGMs); and (c) expressing the repeated measures of a variable as a function of a set of parameters while implying that later observations are a direct function of earlier observations plus some time-specific error (ALTs).

As an example we can examine recent findings on cognitive functioning in patients with schizophrenia. The meta-analysis by Woodberry et al. (2008) suggested that cross-sectional designs can only demonstrate that patients have IQ deficit at different time points but are unable to address the persistent question of whether IQ declines within individuals with illness progression. In response Reichenberg et al. (2010) modelled the cognitive trajectories prior to schizophrenia onset using latent growth curves by utilising the DMHDS sample. This constitutes a sensitive approach in terms of identifying the unique variability in the growth rate of IQ at multiple measurement points with the potential to identify (a) the temporal relationship between IQ decline and illness onset and (b) non-linear trajectories of

developmental deficits. Therefore, Reichenberg and colleagues were able to delineate the differences in the developmental course of various cognitive functions from childhood to early adolescence (Fig. 2) and to identify the pre-morbid decline in executive function associated with schizophrenia. Similar approaches have been successfully applied in other areas of epidemiological research (e.g. Chen et al., 2007).

Despite the availability of longitudinal cohorts epidemiological psychiatric research to date presents with four key limitations. Firstly, examination of critical periods has been limited to narrow developmental windows (instead of taking a life course perspective) and to one or two risk factors (Ben-Shlomo and Kuh, 2002). Secondly, the few studies that have examined accumulation of risk models have been limited primarily by retrospective or cross-sectional data collection (Clemmons et al., 2007; Picken et al., 2010). Thirdly, even studies based on prospective data, have commonly focused on the association between a range of risk factors and outcome. Thus they account only for a relatively small proportion of the total variance and neglect to test for interactions between risk factors. Moreover, the frequent use of composite indices obscures the temporal effects of risk factors and fails to distinguish between critical periods and accumulation of risk (Jaffee et al., 2002; Koenen et al., 2007). Fourthly, there is considerable lack of clarity between measures that constitute risk factors and measures that reflect health outcomes. For example, although cannabis use in adolescence is a risk factor for psychosis (Arseneault et al., 2002; Fergusson et al., 2003), substance abuse can also be considered an adverse diagnostic outcome (Fergusson et al., 1994, 1996; Koenen et al., 2009; Melchior et al., 2007; Woodward and Fergusson, 2001).

4. *Directions for future research*

There has been tremendous progress in our understanding of risk factors and their possible immediate and long-term effects, either independently or in combination. However, there is still much potential for further advancement. We have advocated the benefits of a systematic implementation of life-course models to epidemiological research in psychiatry. This is particularly timely given the recent wider availability of the necessary computational and statistical instruments required. Below we make specific suggestions with regards to the research areas to be prioritised.

A lifecourse approach could advance the field in at least five distinct directions. Firstly, by interrogating available data it would be possible to identify critical periods beyond the early years or life. An example could be exploring the possibility that in women perimenopausal oestrogen decline (Seeman, 2010) may trigger a late “critical period” for the onset of schizophrenia between the ages 45 and 50 years (Häfner, 2005). Secondly, the impact of risk factors may change in magnitude across the lifespan. This has been shown with regards to developmental trajectories for cognitive risk factors in schizophrenia (e.g. Kremen et al., 2008; Reichenberg et al., 2010). Thirdly, Kendler and Gardner (2010) suggested that the effects of interactions of risk factors are of secondary importance to main effects and should be examined only if there is a strong theoretical background. Therefore, modelling of interactions should proceed by testing the robustness of different theoretical assumptions with regards to the timing and conditions under which risk factors may influence disease onset. Fourthly, most studies to date have considered the effect of risk factors on a single outcome. Relatively less is known about the possibility of a particular risk factor increasing the probability for variable outcomes. Such a pluripotent effect of risk factors has been shown for family history of schizophrenia which increases the probability of multiple other adverse mental health outcomes (Dean et al., 2010). Focusing on

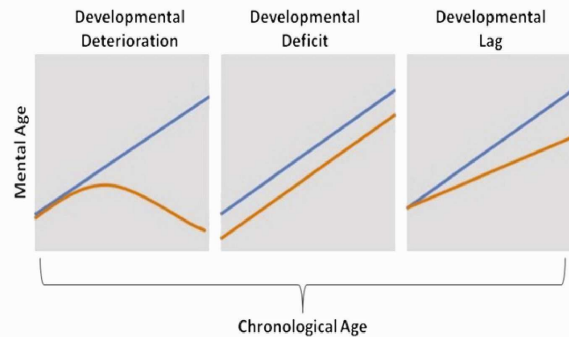


Fig. 2. Differences in the developmental course of cognitive functions from childhood to early adolescence with schizophrenia: an illustrative example.

the variability of outcome has the added advantage that it may lead to identification of protective factors against adverse mental health and will allow modelling future interventions not simply on risk minimisation but also enhancement of resilience. Fifthly, implicit in all current research is the notion that risk factors, particularly those in early life, are “embodied” or in other words, that they produce an irreversible biological changes which then influences adult health outcomes. The logical next step is to identify the relevant biological pathways as a means towards identification of causative mechanisms underlying disease expression. A recent example is provided by Lederbogen et al. (2011) with regards to urbanicity, a factor known to increase the incidence and prevalence of a range of mental disorders. The authors found that urbanicity was associated with increased activation in the amygdala and anterior cingulate cortex during cognitive tasks when they were performed under conditions of social stress (Lederbogen et al., 2011).

In sum, the evidence we have presented points to new avenues in study design and data analysis. It is our view that there are three priority areas, namely (a) modelling and testing pathways showing how risk factors might relate to critical periods of biological development, (b) assessing the cumulative effect following prolonged exposure or the potential clustering with other factors and (c) identifying chains of risk as yet not fully described.

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